OFFICE OF CLINICAL PHARMACOLOGY REVIEW	
NDA Number (SDN)	210251 (641)
Link to EDR	\\CDSESUB1\evsprod\NDA210251\0109
Submission Date	04/09/2021
Submission Type	Efficacy supplement - pediatric
Brand Name	BIKTARVY®
Generic Name	Bictegravir (B or BIC), Emtricitabine (F or FTC), and Tenofovir alafenamide (TAF)
Proposed Dosage Regimen	One tablet (BIC/FTC/TAF; 30/120/15 mg) taken once daily with or without food in patients with body weight at least 14 kg to less than 25 kg
Route of Administration	Oral
Proposed Indication	Treatment of human immunodeficiency virus type 1 (HIV-1) infection
Applicant	Gilead Sciences, Inc.
OCP Review Team	Xing Jing Jihye Ahn Justin C Earp Mario Sampson

Contents

1. Executive Summary

BIKTARVY® is a fixed-dose combination (FDC) of BIC (or B), FTC (or F), and TAF. BIC is an HIV-1 integrase strand transfer inhibitor (INSTI); FTC and TAF are HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs). BIKTARVY® is a complete regimen to treat HIV-1 infected treatment-naive patients or to replace the current antiretroviral regimen in patients who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to any individual components of BIKTARVY®.

The recommended dosage BIKTARVY® is one tablet (BIC/FTC/TAF at 50/200/25 mg) taken orally once daily with or without food in adults. The patient population using this dosing regimen was later expanded to include adolescents [redacted] (b) (4) weighing ≥ 35 kg) and

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children ([redacted] weighing ≥ 25 kg). The approval for these populations was based on data of Cohort 1 (≥ 35 kg) and Cohort 2 (≥ 25 kg) from an open-label Phase 2/3 study GS-US-380-1474.

The Applicant submitted this current Prior Approval Efficacy Supplement to further expand patient population to pediatric patients weighing 14 kg to < 25 kg [redacted] using a lower strength of BIKTARVY® (BIC/FTC/TAF 30/120/15 mg). The Applicant determined that dose-normalized results showed this lower-dose BIC/FTC/TAF [redacted] tablet demonstrated bioequivalence to the approved strength BIC/FTC/TAF 50/200/25 mg bilayer tablet. The recommended dosage regimen is one tablet taken orally once daily with or without food. To support this new expansion and the lower dose, the Applicant provided data of Cohort 3 (HIV-1 infected children ≥ 2 years of age and weighing 14 kg to < 25 kg) in Study GS-US-380-1474.

Pharmacokinetic (PK), safety and efficacy data of Cohort 3 from trial GS-US-380-1474 constitute the totality of evidence supporting the Applicant's proposed dosing regimen for HIV-1 infected pediatric patients [redacted] weighing 14 kg to < 25 kg. The observed or estimated differences in exposure between Cohort 3 and adults and/or Cohorts 1-2 were not clinically significant. The current submission fulfills the postmarketing requirement (PMR) 3322-1 which required conducting a study in pediatric patients 2 to <18 years old.

2. Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined this pediatric efficacy supplement is approvable from a clinical pharmacology perspective. The key review issues, specific recommendations, and comments are summarized below.

3. Labeling Updates

Clinical pharmacology related labeling updates and comments are summarized below:

Heading (Section)	Updates (Bold) and Comments
INDICATIONS AND USAGE (1)	BIKTARVY is a three-drug combination of bictegravir (BIC), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients [redacted] **weighing at least 14 kg** ~~**25 kg**~~ who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of

	treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.
DOSAGE AND ADMINISTRATION (2.3) in HIGHLIGHTS OF PRESCRIBING INFORMATION	**Recommended dosage in pediatric patients (b) (4) weighing at least 14 to less than 25 kg: One 30 mg/120 mg/15 mg tablet taken once daily with or without food. (2.3)**
Recommended Dosage in Pediatric Patients (b) (4) Weighing at Least 14 to Less than 25 kg (2.3)	**2.3 Recommended Dosage in Pediatric Patients (b) (4) Weighing at Least 14 to Less than 25 kg** **The recommended dosage of BIKTARVY is one tablet containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF taken orally once daily with or without food in:** **• pediatric patients (b) (4) weighing at least 14 to less than 25 kg, and estimated creatinine clearance greater than or equal to 30 mL per minute** **[see Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)].**
DOSAGE FORMS AND STRENGTHS (3)	Tablets: 50 mg/200 mg/25 mg, **30 mg/120 mg/15 mg** of bictegravir, emtricitabine, and tenofovir alafenamide, (b) (4).
USE IN SPECIFIC POPULATIONS (8.4)	(b) (4)
Pharmacokinetics (12.3)	**Table 8 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects at Least 2 Years of Age and Weighing at Least 14 to Less than 25 kg**

Note: the bolded texts in the table represent the labeling updates proposed by the Applicant.

Reviewer's comments:

1. *The youngest participants in the clinical Study GS-US-380-1474 were 3 years old and lowest body weight was 14 kg.* (b) (4) *and this approach is being applied for BIC/FTC/TAF.*
2. *In section 2.3, the Applicant proposed that recommended BIC/FTC/TAF dosing was for patients ≥ 14 kg with estimated creatinine clearance ≥ 30 mL/min. Renal function estimation using creatinine clearance is only appropriate for adults. We recommend using the term estimated glomerular filtration rate (eGFR [mL/min/1.73m^2]), for assessment of renal functions for eligible pediatrics patients.*
3. *Due to issues with performance of the TAF population PK model for estimation of PK parameters in subjects weighing ≥ 14 kg to less than 25 kg, we requested that the Applicant show PK parameters based on intensive sampling* (b) (4)

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4. Key Clinical Pharmacology Review Question(s)

Is the proposed dosing regimen appropriate for pediatric patients with body weight at least 14 kg to less than 25 kg for which the indication is being sought?

Yes, we agree that the proposed dosing regimen, 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF, is appropriate for pediatric patients with body weight ≥ 14 kg (< 25 kg) for which the indication is being sought. The review team evaluated the information described below to determine the acceptability of the proposed dosing regimen.

Given the combination of sparse and intensive PK sampling, the Applicant utilized a population PK (PopPK) approach to the estimation of BIC and TAF exposures. To this end, the Applicant developed a PopPK model using the data from HIV-1 infected pediatric patients. The systemic exposures of BIC and TAF projected by the PopPK model and the systemic exposure of FTC calculated via the intensive concentration data for Cohort 3 were compared with those from BIC/FTC/TAF treated, HIV-1 infected adult subjects in the Phase 3 studies.

In addition, the reviewer compared the distributions of BIC, TAF, and FTC C_{max}, AUC_{tau}, and C_{tau} between adults and Cohorts1-3 (Note: the approval for NDA210251 SDN 234 was based on data from Cohort 1 and 2). The reviewer's analysis utilized the Applicant's Study GS-US-380-1474 pp datasets (NDA 210251, SN 0050 and SN 0109) for Cohorts 1-3, which contain intensive PK parameters.

PK Comparison for BIC

For BIC, the plasma PK parameters of cohort 3 and the comparisons with those in adults using the PopPK analysis set and the intensive PK analysis set are shown in Table 1a and Table 1b, respectively. In addition, the Applicant compared PK parameters of BIC between children in Cohort 3 (Part A) and adolescent subjects and children in Cohorts 1 and 2 (Part A), as shown in Table 1c.

Table 1a Comparisons of BIC Plasma PK Parameter Estimates Between Cohort 3 and Adults (PopPK Analysis Set)

	Mean (%CV)		
BIC PK Parameter	GS-US-380-1474 (Test) (N = 22)	GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878 (Reference) (N = 1193)	%GLSM Ratio (90% CI) Test/Reference
AUC_{tau} (h•ng/mL)	126086.8 (42.4)	102001.0 (26.9)	118.19 (102.15, 136.76)
C_{max} (ng/mL)	9147.0 (44.8)	6145.8 (22.9)	138.60 (117.61, 163.34)
C_{tau} (ng/mL)	2434.6 (40.1)	2609.9 (35.2)	93.34 (82.58, 105.51)

Source: Table 2 in the Applicant's Summary of Clinical Pharmacology (available at: \\CDSESUB1\evsprod\NDA210251\0109\m2\27-clin-sum\summary-clin-pharm.pdf)
Note: PopPK parameters for the test group were from cohort 3 in study GS-US-380-1474; N = 22. PopPK parameters for the reference group were from BIC/FTC/TAF-treated adults in studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878; N = 1193. Cohort 3: ≥ 3 years of age, weighing ≥ 14 to < 25 kg (same for below tables).

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Table 1b Comparisons of BIC Plasma PK Parameter Estimates Between Cohort 3 and Adults (Intensive PK Analysis Set)

PK Analyte Parameter (units)	GLSM (n)		%GLSM Ratio (90% CI) Test/Reference
	GS-US-380-1474 Cohort 3 Part A (Test)	GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, Adult Intensive PK (Reference)	
Bictegravir			
AUC_{tau} (h•ng/mL)	105891.98 (12)	89032.20 (77)	118.94 (105.02, 134.70)
C_{max} (ng/mL)	9856.72 (12)	6506.13 (77)	151.50 (135.35, 169.58)
C_{tau} (ng/mL)	1604.83 (11)	2028.27 (75)	79.12 (58.39, 107.22)

Source: Table 1 in the Applicant's response to clinical pharmacology information request (available at: \\CDSESUB1\evsprod\NDA210251\0119\m1\us\111-information-amendment\efficacy.pdf)
Note: PK parameters for the test group were calculated via concentration data from cohort 3 (part A) in study GS-US- 380-1474; N = 12 (N = 11 for C_{tau}). Intensive PK parameters for the reference group were from BIC/FTC/TAF-treated adults in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878; N = 77 (N = 74 for C_{tau}).

Table 1c Comparisons of BIC Plasma PK Parameters Between Cohort 3 and Cohort 1 & 2 (Intensive PK Analysis Set)

Cohort 3 (Test) vs Cohort 1 and 2 (Reference)				
	Test	Reference	Test/Reference % (90% CI)	rMSE
AUC_{tau} (h·ng/mL)	105891.98 (N=12)	109747.05 (N=49)	96.49 (84.64,109.99)	0.316
C_{max} (ng/mL)	9856.72 (N=12)	9119.19 (N=49)	108.09 (95.64,122.15)	0.309
C_{tau} (ng/mL)	1604.83 (N=11)	2011.44 (N=48)	79.79 (57.98,109.78)	0.578
Cohort 3 (excluding subject 07546-7304) vs Cohort 1 and 2				
	Test	Reference	Test/Reference % (90% CI)	rMSE
AUC_{tau} (h·ng/mL)	106837.70 (N=11)	109747.05 (N=49)	97.35 (84.75,111.82)	0.316
C_{max} (ng/mL)	9920.66 (N=11)	9119.19 (N=49)	108.79 (95.59,123.82)	0.309
C_{tau} (ng/mL)	1660.66 (N=10)	2011.44 (N=48)	82.56 (58.66,116.19)	0.597

Information source: Table Req12745.2.6.1 in the Applicant's study report for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf)
Note: Cohort 1: 12 to < 18 years of age, weighing ≥ 35 kg; Cohort 2: 6 to < 12 years of age, weighing ≥ 25 kg (same for below tables).

Table 1d Summary Statistics of BIC PK Parameters in Cohort 3 and Cohort 1 & 2 and Adults (PopPK Analysis Set)

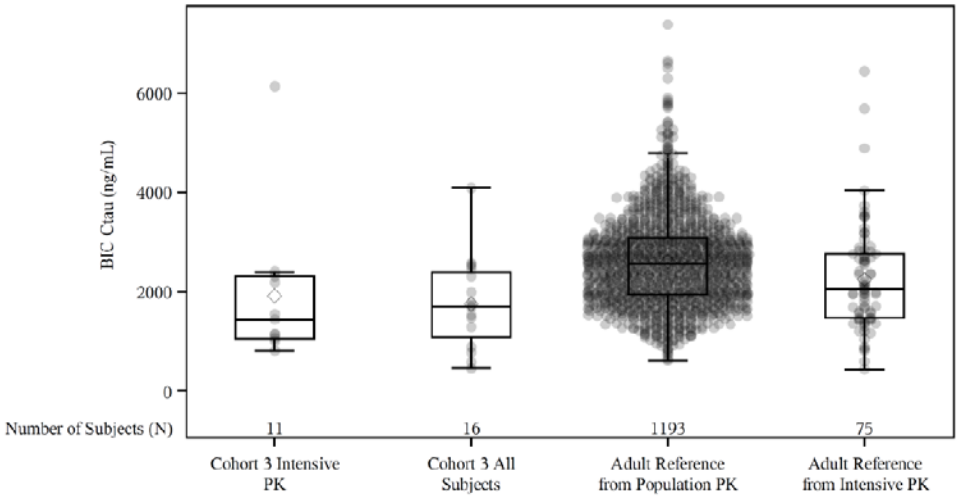
PK Parameters	Cohort 3		Cohort 1		Cohort 2		Adults	
	Min	Max	Min	Max	Min	Max	Min	Max
C_{max} (ng/mL)	2880.0	20000.0	4890.0	14500.0	6300.0	20500.0	2724.3	11761.6
AUC_{tau} (h·ng/mL)	46646.0	285203.0	56875.0	185571.2	66800.8	214684.4	43185.4	230414.7
C_{tau} (ng/mL)	1166.1	5804.9	768.0	5660.0	670.0	9180.0	604.9	7396.8

Information source: study reports for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf; and at: \\CDSESUB1\evsprod\NDA210251\0050\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf) and summary of clinical pharmacology (available at: \\CDSESUB1\evsprod\nda210251\0109\m2\27-clin-sum\summary-clin-pharm.pdf)

Based on BIC PopPK analysis set, mean BIC C_{max}, AUC_{tau} and C_{tau} were 38.6% higher, 18.2% higher, and 6.7% lower, respectively, in Cohort 3 pediatrics compared with those PK parameters in adults. Based on BIC intensive PK analysis set, these figures are 51.5% higher, 18.9% higher, and 20.9% lower. The lower C_{tau} (based on intensive PK) is not considered a clinical efficacy concern, because 1) BIC C_{tau} values in Cohort 3 are within the range of BIC C_{tau} values in adults (Figure 1a and Table 1d) and the range of Cohort 1 and 2 (Figure 1b); 2) 100% of subjects (N =20) with virological data in Cohort 3 achieved virologic outcome (HIV-1 RNA < 50 copies/mL at Week 24.

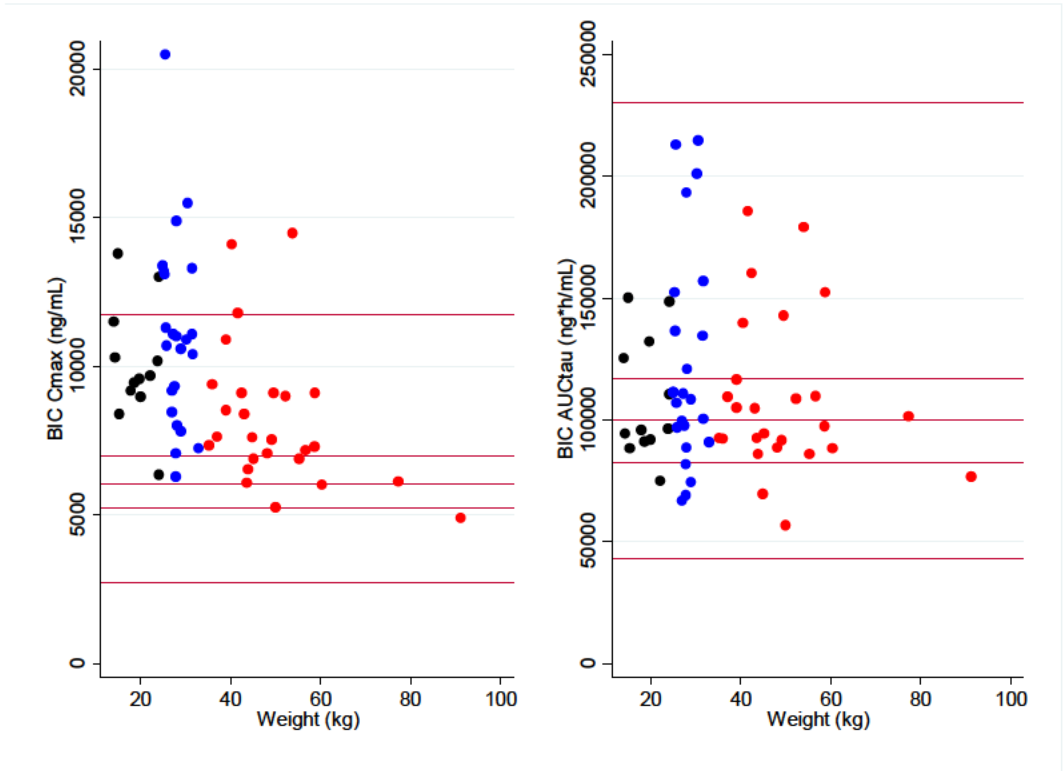
The higher BIC C_{max} is not considered clinically significant because 1) Cohort 3 exposures are comparable to and within the range of those of Cohort 1 and 2 (Table 1c and Figure 1b); 2) In Cohort 3, the majority of AEs reported were Grade 1. No Grade 3 or 4 AEs were reported. Adverse events (AEs) considered related to study drug were reported for 13.6% (3 of 22) of subjects. None of study drug-related AEs was reported by more than one subject; 3) There lacks a positive exposure-safety or exposure-efficacy relationship for BIC and TAF in Cohort 1 and 2 in study GS-US-380-1474, as determined by a previous clinical pharmacology review (checked in DARRTs May 23, 2019, for NDA210251 SDN234). (Note: the BIC PK estimated by PopPK analysis will be used in the label to match the section for Cohort 1 and 2 in the label)

Figure 1a Box Plots Comparing BIC Ctau Across Cohort 3 Intensive PK, Cohort 3 All Subjects, Adult Reference from Population PK, and Adult Reference from Intensive PK



Source: Figure 1 in the Applicant's response to clinical pharmacology information request (available at: \\CDSESUB1\evsprod\NDA210251\0119\m1\us\111-information-amendment\efficacy.pdf)

Figure 1b Comparison of the BIC C_{max} and AUC_{tau} Distributions Between Cohort 3 and Adults and Cohort 1 & 2 (Intensive PK Analysis Set)



Note: Plotted by reviewer. The red lines represent the min, Q1, median, Q3, and max values of adult data (from studies indicated in Table 1b). Red, blue, and black dots represent Cohort 1, 2, and 3 data.

PK Comparison for TAF

For TAF, the plasma intensive PK parameters of Cohort 3 and the comparisons with intensive PK in adults are shown in Table 2a. Pharmacometric assessment noted the following limitations of the Applicant's PopPK analysis for TAF: 1) significant discrepancy in the model-estimated Cohort 3 exposure metrics (C_{max}, AUC_{tau}) compared to those estimated from intensive PK sampling, and 2) model reproducibility issue due to unsuccessful minimizations. (b) (4)

[redacted]

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Table 2a Comparisons of TAF Plasma PK Parameter Estimates Between Cohort 3 and Adults (Intensive PK Analysis Set)

	GLSM		
TAF PK Parameter	GS-US-380-1474 (Test) (N = 12)	GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878 (Reference) (N = 77)	%GLSM Ratio (90% CI) Test/Reference
AUC_{tau} (h•ng/mL)	281.67	194.64	144.71 (114.94, 182.20)
AUC_{last} (h•ng/mL)	279.71	192.48	145.32 (115.33, 183.11)
C_{max} (ng/mL)	392.76	227.18	172.89 (139.83, 213.76)

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Source: Table 56 in the Applicant's study report for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf)
Note: PK parameters for the test group were calculated via concentration data from cohort 3 (part A) in study GS-US- 380-1474; N = 12. Intensive PK parameters for the reference group were from BIC/FTC/TAF-treated adults in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878; N = 77.

Table 2b Comparisons of TAF Plasma PK Parameters Between Cohort 3 and Cohort 1 & 2 (Intensive PK Analysis Set)

Cohort 3 (Test) vs Cohort 1 and 2 (Reference)				
	Test	Reference	Test/Reference % (90% CI)	rMSE
AUC_{tau} (h·ng/mL)	281.67 (N=12)	300.73 (N=45)	93.66 (72.23,121.45)	0.650
AUC_{last} (h·ng/mL)	279.71 (N=12)	299.37 (N=48)	93.43 (72.31,120.73)	0.649
C_{max} (ng/mL)	392.76 (N=12)	311.33 (N=48)	126.16 (96.21,165.42)	0.868
Cohort 3 (excluding subject 07546-7304) vs Cohort 1 and 2 (excluding subject 07547-7126)				
	Test	Reference	Test/Reference % (90% CI)	rMSE
AUC_{tau} (h·ng/mL)	274.19 (N=11)	287.89 (N=44)	95.24 (73.23,123.87)	0.587
AUC_{last} (h·ng/mL)	272.18 (N=11)	287.37 (N=47)	94.71 (73.01,122.86)	0.590
C_{max} (ng/mL)	381.82 (N=11)	299.31 (N=47)	127.56 (97.16,167.48)	0.833

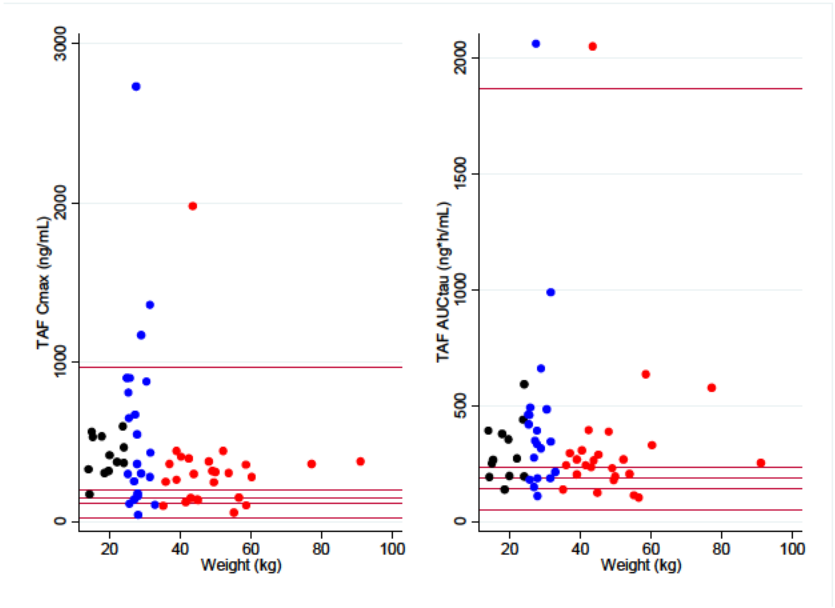
Information source: Table Req12745.2.6.2 in the Applicant's study report for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf)

Table 2c Summary Statistics of TAF PK Parameters in Cohort 3 and Cohort 1 & 2 and Adults (Intensive PK Analysis Set)

PK Parameters	**Cohort 3**		**Cohort 1**		**Cohort 2**	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**
C_{max} (ng/mL)	168.0	599.0	55.7	443.0	41.4	2730.0
AUC_{tau} (h·ng/mL)	138.1	593.0	104.3	635.1	109.3	2061.9

Information source: study reports for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf; and at: \\CDSESUB1\evsprod\NDA210251\0050\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf) and summary of clinical pharmacology (available at: \\CDSESUB1\evsprod\nda210251\0109\m2\27-clin-sum\summary-clin-pharm.pdf)
Note: The summary for adult data are not available.

Figure 2 Comparison of the TAF C_{max} and AUC_{tau} Distributions Between Cohort 3 and Adults and Cohort 1 & 2 (Intensive PK Analysis Set)



Note: Plotted by reviewer. The red lines represent the min, Q1, median, Q3, and max values of adult data (from studies indicated in Table 1b). Red, blue, and black dots represent Cohort 1, 2, and 3 data.

Mean TAF AUC_{tau} and C_{max} were 44.7% and 72.9% higher, respectively, in Cohort 3 pediatrics than in BIC/FTC/TAF-treated HIV-1 infected adult subjects in historical studies. These higher exposure values are not considered clinically significant because 1) The range of Cohort 3 exposures are within the range of exposures in adults and Cohort 1 and 2 (Table 2c and Figure 2); 2) Exposures (AUC) in Cohort 3 are comparable to Cohort 1 and 2 (Table 2b); 3) The safety results in Cohort 3 as described above for BIC.

PK Comparison for FTC

The plasma FTC intensive PK parameters of Cohort 3 and the comparisons with intensive PK in adults are shown in Table 3. (Note: FTC population PK model is not developed.)

Table 3a Comparisons of FTC Plasma PK Parameter Estimates Between Cohort 3 and Adults (Intensive PK Analysis Set; Cohort 3 Part A)

	Mean (%CV)		
FTC PK Parameter	**GS-US-380-1474 (Test) (N = 12[a])**	**GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878 (Reference) (N = 77[b])**	**%GLSM Ratio (90% CI) Test/Reference**
AUC_{tau} (h•ng/mL)	14991.2 (21.9)	12293.6 (29.2)	124.76 (111.79, 139.23)
C_{max} (ng/mL)	3849.2 (34.7)	2127.0 (34.7)	181.12 (150.12, 218.52)
C_{tau} (ng/mL)	210.3 (242.9)	96.0 (37.4)	82.60 (47.69, 143.07)

Source: Table 3 in the Applicant's Summary of Clinical Pharmacology (available at: \\CDSESUB1\evsprod\NDA210251\0109\m2\27-clin-sum\summary-clin-pharm.pdf)

Note: PK parameters for the test group were calculated via concentration data from cohort 3 (part A) in study GS-US- 380-1474; N = 12 (N = 11 for C_{tau}). Intensive PK parameters for the reference group were from BIC/FTC/TAF-

treated adults in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878; N = 77 (N = 74 for C_{tau}).

Table 3b Comparisons of FTC Plasma PK Parameters Between Cohort 3 and Cohort 1 & 2 (Intensive PK Analysis Set)

Cohort 3 (Test) vs Cohort 1 and 2 (Reference)				
	Test	Reference	Test/Reference % (90% CI)	rMSE
AUC_{tau} (h·ng/mL)	14708.44 (N=12)	14953.11 (N=49)	98.36 (87.54,110.53)	0.282
C_{max} (ng/mL)	3629.60 (N=12)	3083.01 (N=49)	117.73 (96.54,143.57)	0.380
C_{tau} (ng/mL)	74.25 (N=11)	72.92 (N=48)	101.82 (57.54,180.17)	1.086
Cohort 3 (excluding subject 07546-7304) vs Cohort 1 and 2				
	Test	Reference	Test/Reference % (90% CI)	rMSE
AUC_{tau} (h·ng/mL)	14576.11 (N=11)	14953.11 (N=49)	97.48 (86.19,110.25)	0.282
C_{max} (ng/mL)	3472.79 (N=11)	3083.01 (N=49)	112.64 (92.44,137.27)	0.380
C_{tau} (ng/mL)	80.00 (N=10)	72.92 (N=48)	109.71 (59.54,202.15)	1.115

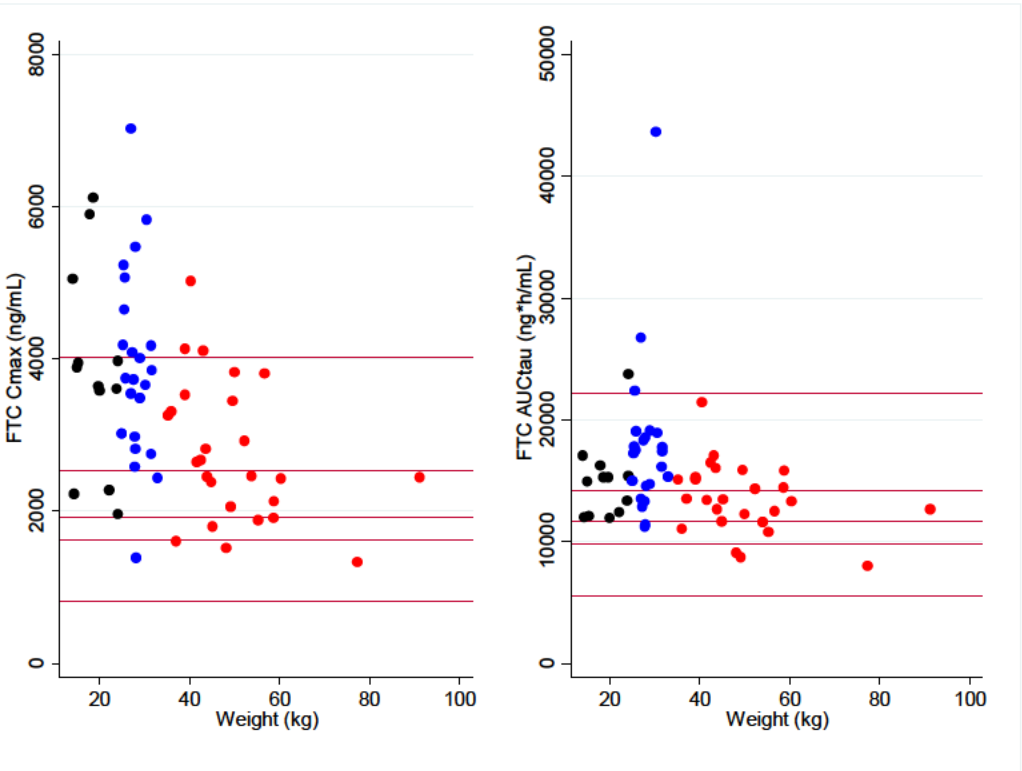
Information source: Table Req12745.2.6.4 in the Applicant's study report for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf)

Table 3c Summary Statistics of FTC PK Parameters in Cohort 3 and Cohort 1 & 2 and Adults (Intensive PK Analysis Set)

PK Parameters	Cohort 3		Cohort 1		Cohort 2		Adults	
	Min	Max	Min	Max	Min	Max	Min	Max
C_{max} (ng/mL)	1960.0	6120.0	1330.0	5030.0	1390.0	7020.0	822.0	4030.0
AUC_{tau} (h·ng/mL)	11961.3	23740.1	8034.2	21428.1	11077.7	43640.0	5602.3	22198.8
C_{tau} (ng/mL)	34.5	1750.0	30.2	91.6	37.3	3660.0	39.5	217.0

Information source: study reports for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf; \\CDSESUB1\evsprod\NDA210251\0050\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf) and summary of clinical pharmacology (available at: \\CDSESUB1\evsprod\nda210251\0109\m2\27-clin-sum\summary-clin-pharm.pdf)

Figure 3 Comparison of the FTC C_{max} and AUC_{tau} Distributions Between Cohort 3 and Adults and Cohort 1 & 2 (Intensive PK Analysis Set)



Note: Plotted by reviewer. The red lines represent the min, Q1, median, Q3, and max values of adult data (from studies indicated in Table 1b). Red, blue, and black dots represent Cohort 1, 2, and 3 data.

The 81.1% higher FTC C_{max} and 24.8% higher FTC AUC_{tau} values compared to adult subjects are not considered clinically significant, because 1) The FTC exposures in Cohort 3 are comparable to Cohort 1 and 2 (Table 3b), and the range of Cohort 3 C_{max} and AUC_{tau} values are within the range in Cohort 2 (Table 3c and Figure 3); 2) the safety results in Cohort 3 as described above.

The mean 17.4% lower FTC C_{tau} values in Cohort 3 compared to adult subjects are not considered clinically significant because all values are within the range observed in Cohort 1 (Figure 4).

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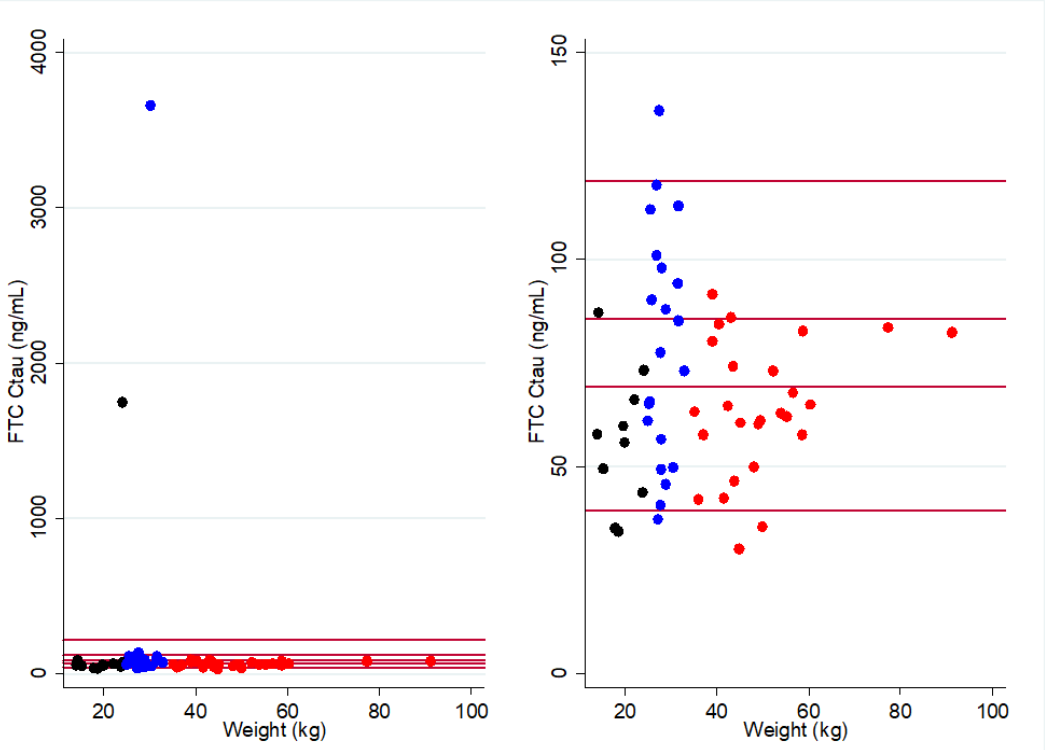
Figure 4 Comparison of the FTC C_{tau} Distributions Between Cohort 3 and Adults and Cohort 1 & 2 (Intensive PK Analysis Set)



Note: Plotted by reviewer. The figure on the left includes all values; two outliers with values > 2000 ng/mL are not included in the figure on the right. The red lines represent the min, Q1, median, Q3, and max values of adult data (from studies indicated in Table 1b). Red, blue, and black dots represent Cohort 1, 2, and 3 data.

5. Individual Study Review

GS-US-380-1474 (EDR Link)
Note: this review only focuses on the clinical pharmacology aspects and Cohort 3 of this trial. The clinical pharmacology of Cohort 1 and Cohort 2 data of this study has been previously reviewed (checked in DARRTs May 23, 2019, for NDA210251 SDN234).

Title: A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) Fixed Dose Combination (FDC) in HIV-1 Infected Adolescents and Children. (Note: GS-9883 refers to BIC)

Study Period: 09/21/2016 to 06/25/2020

Objectives (Cohort 3):

Primary:
Part A: To evaluate the steady state PK of BIC and confirm the dose of B/F/TAF 30/120/15 mg FDC in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.

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Parts A and B: To evaluate the safety and tolerability of the low dose B/F/TAF FDC tablet through Week 24 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.

Secondary:
Parts A and B: To evaluate the safety, tolerability and antiviral activity of the low dose B/F/TAF FDC tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.

Main Inclusion Criteria (Cohort 3):

- ≥ 2 years of age, weight ≥ 14 to < 25 kg;
- Virologically suppressed (HIV-1 RNA < 50 copies/mL or undetectable HIV-1 RNA if the limit of detection of the local assay used was ≥ 50 copies/mL) for ≥ 6 months prior to screening on a stable antiretroviral regimen comprising 2 nucleoside reverse transcriptase inhibitors plus a third agent;
- Estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2 (as calculated using the Schwartz formula; eGFRSchwartz) at screening;
- No documented or suspected resistance to FTC, tenofovir (TFV), or integrase strand-transfer inhibitors including, but not limited to, the reverse transcriptase resistance mutations K65R and M184V/I.

Test Product, Dose and Mode of Administration (Cohort 3):

FDC tablet of B/F/TAF (30/120/15 mg) administered orally, once daily, without regard to food.

Clinical Pharmacology Reviewer's Note:
In Cohort 3 (N=22) of Study GS-US-380-1474, all subjects swallowed either the intact tablet (N=17 at Day 1) or all the pieces of the split-in-half tablets (N=5 at Day 1). Since the proposed product is formulated as immediate release (b) (4) *tablets* (b) (4) *and the clinical review team has no concern with splitting the tablet from an efficacy standpoint, Biopharmaceutics review team has no concern with breaking/cutting/chewing on the tablet (in any number and shape of pieces) before swallowing, as long as all pieces of the whole tablet are administrated at the same time or within a short period of time.*

Trial Design:

Study GS-US-380-1474 is an ongoing, open-label, multicenter, multicohort, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of the B/F/TAF FDC in HIV-1 infected pediatric subjects. A total of 20 children (cohort 3: ≥ 2 years of age) were planned to be enrolled (Figure 5).

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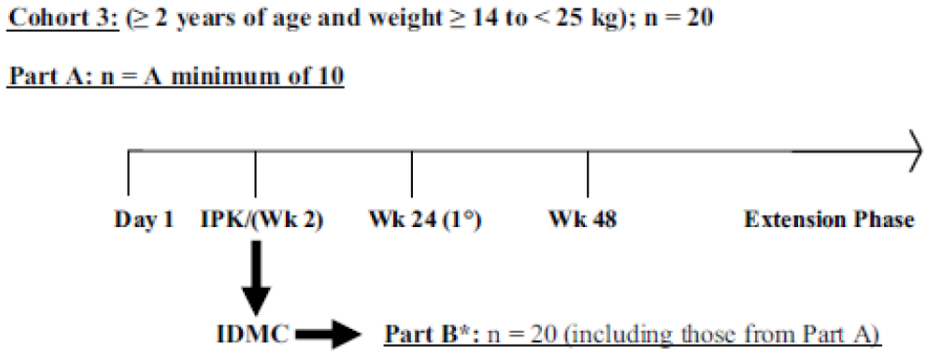
Figure 5 Study Scheme for Cohort 3



Source: Figure 1 in the Applicant's study report for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf)

Note: Part B determined by the Applicant based on Part A results.
IDMC = independent data monitoring committee; IPK = intensive pharmacokinetic sampling; Wk = week
Source: Figure 1 in the Applicant's study report for GS-US-380-1474 (available at: \\CDSESUB1\evsprod\NDA210251\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-380-1474\report-body.pdf)

Bioanalytical method:

The precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration.

Results (Cohort 3):

Main Subject Demographics and Baseline Disease Characteristics

- Number of Subjects: enrolled: 22, full PK analysis set: 22, intensive PK set: 12.
- 50% subjects were female.
- Median age: 6 (3 to 9) years.
- The median (Q1, Q3) and mean (min, max) baseline body weight values were 18.7 kg (Q1=15.2, Q3=21.7) and 18.8 kg (min=14.1, max=24.1), respectively.
- Race: 72.7% of subjects were black and 22.7% of subjects were Asian, and 100.0% were not Hispanic or Latino.
- All subjects had baseline plasma HIV-1 RNA < 50 copies/mL.
- Median (Q1, Q3) baseline $eGFR_{Schwartz}$ was 160.5 (145.0, 168.0) mL/min/1.73 m^2.

Pharmacokinetics (Cohort 3):

The PK parameters for BIC, FTC, and TAF in pediatric patients in Cohort 3 of pediatric study GS-US-380-1474 are summarized in Table 5. Compared to the results in adults, no differences in PK are deemed clinically significant (please refer to Key Clinical Pharmacology Review Question, subsection 4 for details).

Table 5 Multiple Dose PK Parameters of BIC, FTC and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects of Cohort 3 in Study GS-US-380-1474

Parameter Mean (CV%)	BIC [a]	BIC [b]	FTC [b]	TAF [b]
C_{max} (ng/mL)	9147.0 (44.8)	10040.0 (19.9)	3849.2 (34.7)	413.8 (31.0)
AUC_{tau} (h•ng/mL)	126086.8 (42.4)	108364.5 (22.9)	14991.2 (21.9)	305.4 (42.6)
C_{trough} (ng/mL)	2434.6 (40.1)	1924.5 (78.3)	210.3 (242.9)	N/A

CV = Coefficient of Variation; N/A = Not Applicable (C_{trough} is not reported for TAF)
a. From Population PK analysis (N=22).
b. From Intensive PK analysis (N=12).

Data Integrity-Related Consults (OSIS Inspections)

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for this application. The OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: Non Responsive . The final classification for the inspection was No Action Indicated (NAI).

Conclusions

• No clinically relevant differences in BIC/FTC/TAF exposure parameters were observed in pediatric subjects weighing at least 14 kg to less than 25 kg from those in adults.
• The BIC/FTC/TAF exposure data submitted in this study report support the use of BIC/FTC/TAF 30/120/15 mg for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg to less than 25 kg.

Reviewer's Overall Assessment

The study design, results and conclusions are acceptable.

6. Pharmacometrics Review

Pharmacometrics reviewer reviewed following reports:

Report No.	Title	Referred to as in this review
(b) (4)-2020-1050 BIC Peds Pop PK	Population Pharmacokinetic Analysis of Bictegravir in HIV-1 Infected Adolescents and Children	BIC peds PopPK report
(b) (4)-2020-1048 TAF-TFV Peds Pop PK	Population Pharmacokinetic Analysis of Tenofovir Alafenamide and Tenofovir Following Administration of Tenofovir Alafenamide Containing–Fixed-Dose	TAF/TFV peds PopPK report

Reference ID: 4857658

	Combinations in HIV-1 Infected Adolescents and Children	
Applicant's Response to IR received on 8/7/2021	Response to Clinical Pharmacology Information Request (Comment 3) dated 02 July 2021	Applicant's Response to IR

6.1 Review Summary

Applicant's PopPK analysis of bictegravir (BIC) is acceptable in describing the observed BIC PK in pediatric patients aged 3 years and older and with body weight >14.1 kg. Parameters were estimated with acceptable precision with %RSE for fixed-effect parameters generally <30%. The GOF plots show agreement between the predicted concentrations and observed concentrations in all three cohorts in Study GS-US-380-1474. The GOF plots in the subgroup of body weight 14 to <25kg did not show any unacceptable bias. The magnitude of ETA shrinkage of the final PPK model was small (<15%) for CL/F, and Vc/F. The model-derived BIC exposures at steady-state for pediatric patients weighing 14 to <25 kg receiving B/F/TAF 30/120/15 mg FDC are comparable with those observed in adult patients receiving B/F/TAF 50/200/25 mg FDC.

The noted limitations of the Applicant's PopPK analysis for tenofovir alafenamide (TAF) are 1) significant discrepancy in estimated exposure metrics compared to those derived from intensive PK sampling, and 2) model reproducibility due to unsuccessful minimizations due to rounding error. (b) (4)

The Applicant's PopPK analysis of tenofovir (TFV) reasonably describes the observed TFV PK in pediatric patients age 3 years old and with body weight >14.1 kg and is considered adequate to derive individual exposure metrics for pediatric patients receiving BIKTARVY. TFV model was a sequential model using individual PK estimates from the TAF PopPK model as input. The limitations noted in TAF model appears to minimally impact the PK parameter estimates for TFV. The model-derived TFV exposures at steady state for pediatric patients weighing 14 to <25 kg receiving BIC/F/TAF 30/120/15 mg FDC are comparable with those weighing ≥25 kg receiving B/F/TAF 50/200/25 mg FDC.

6.2 Bictegrevir (BIC)

Reviewer's note: A pediatric PopPK model for BIC (Report# QP-2018-1028 BIC HIV Pediatric Pop PK) was previously submitted to support the previous submission NDA210251 S5 (SD234) for one tablet (B/F/TAF; 50/200/25 mg) taken once daily with or without food in patients with body weight at least 25 kg. Division of Pharmacometrics has reviewed this model and determined the model was acceptable to estimate the steady-state exposures in pediatric patients for comparison with adult exposures. The Applicant further updated the model with additional pediatric PK data collected from Cohort 3 from Study GS-US-380-1474 (See Section 5 for the study design).

Data: Study GS-US-380-1474 was the only study included this analysis to evaluate the PK. Cohorts 1 and 2 (adolescents [12 to < 18 years of age] and children [6 to <12 years of age])

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received B/F/TAF 50/200/25 mg FDC, and Cohort 3 (children ≥ 2 years of age weighing ≥14 to <25 kg) received B/F/TAF 30/120/15 mg. The PopPK analysis dataset included 1247 samples from 122 subjects with at least 1 measurable concentration. A total of 13 samples were BLQ and therefore excluded from the analysis. Thus, 1234 BIC concentrations from 122 subjects were used in the PopPK analysis. The analysis population was primarily black (69%), and Asian (24%) with a median (range) age of 11 (3, 17) years and weight of 34 (14.1, 123) kg. A total of 57.4% of patients were female subjects.

Table 6 Summaries of continuous and categorical covariates of the BIC PopPK analysis population

Subject Characteristic	Statistics	N = 122	
Age (years)	Mean (SD)	10.8 (3.76)	
	Median [Min, Max]	11.0 [3.00, 17.0]	
Weight (kg)	Mean (SD)	37.6 (18.0)	
	Median [Min, Max]	34.0 [14.1, 123]	
BMI (kg/m^2)	Mean (SD)	18.6 (5.04)	
	Median [Min, Max]	17.7 [12.6, 45.7]	
BSA (m^2)	Mean (SD)	1.19 (0.333)	
	Median [Min, Max]	1.14 [0.590, 2.37]	
BCLCRSW (mL/min/1.73 m^2)	Mean (SD)	156 (29.0)	
	Median [Min, Max]	151 [89.0, 259]	
Sex		Male	52 (42.6%)
		Female	70 (57.4%)
Race		White	3 (2.5%)
		Black	84 (68.9%)
		Asian	29 (23.8%)
		Other	6 (4.9%)
Coadministration of P-gp inhibitor		No	109 (89.3%)
		Yes	13 (10.7%)
Coadministration PPIs		No	120 (98.4%)
		Yes	2 (1.6%)

Source: Applicant's BIC peds PopPK report. Table 6 and Table 7. Page 23-24.

Base model: The previously submitted model was a 1-compartment model with first-order absorption and lag time was used as starting point for modeling to describe the extended pediatric data. This model included fixed allometric scaling on clearance and volume of distribution and the effect of proton-pump inhibitor (PPI) on Ka, which was fixed to the value estimated in adults. The model fit the log of BIC concentrations with a proportional residual error model. As the additional of an additive residual error component decreased the objective function value (OFV) by ~300, the combined residual error model was retained in the base model. Interindividual variability (IIV) in the PK parameters was 35% and 52% for oral clearance and volume.

Covariate Analysis: Only WT was found to show significant ($p < 0.01$) trends with PK parameters in the screening step. However, the covariates of interest in the previous analysis

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(body weight, age, race, and coadministration with a P-gp inhibitor) were carried forward for further examination.

Final model: Asian race on CL/F (-26.9%) and Vc/F (-27.2%) was found to be significant during the stepwise covariate modeling search. No additional covariates were found to significantly affect BIC exposure. Addition of correlation between CL/F and Vc/F was found to significantly improve the model fit. IIV was included on CL/F and Vc/F and a combination of additive and proportional error model was used. The final parameter estimates for the final BIC PPK model are presented in Table 7 and the standard GOF plots and prediction-corrected visual predictive check (pcVPC) plots were presented in Figure 6 and Figure 7. ETA shrinkages were 7.2% (for CL/F) and 14.5% (for Vc/F).

Table 7 Parameter Estimates for the final BIC PopPK model

Parameter	Parameter Description		Population Estimate	Change from Typical (%)	IIV (%)
$\exp(\theta_3)$	Apparent oral clearance, CL/F (L/h)	Non-Asian	0.453	–	36
$\exp(\theta_3) \times (1+\theta_8)$		Asian	0.331	-26.9	–
$\exp(\theta_3) \times ((\frac{WT}{34})^{0.75})$	Influence of WT on CL/F	5th %ile of WT	0.248	-45.3	–
	Influence of WT on CL/F	95th %ile of WT	0.762	68	–
$\exp(\theta_4)$	Apparent central volume, V_c/F (L)	Non-Asian	9.62	–	52
$\exp(\theta_4) \times (1+\theta_9)$		Asian	7.01	-27.2	–
$\exp(\theta_4) \times ((\frac{WT}{34})^{1})$	Influence of WT on V_c/F	5th %ile of WT	4.31	-55.2	–
	Influence of WT on V_c/F	95th %ile of WT	19.2	99.7	–
$\exp(\theta_5)$	First-order absorption rate constant, k_a (1/h)	without PPI	2.88	–	–
$\exp(\theta_5) \times (1+\theta_7)$		with PPI	1.26	-56.3	–
$\exp(\theta_6)$	Absorption lag time, ALAG1 (h)		0.383	–	–
$\sqrt{\theta_1}$	Residual proportional error (%)		37	--	--
θ_2	Residual additive		1580	–	–

Source: Applicant's BIC peds PopPK report. Table 10. Page 28. Typical subject was a 34-kg, Non-Asian pediatric subject receiving B/F/TAF. The 5th and 95th percentile of WT are 15 and 68 kg. The terminal $t_{1/2}$ was calculated as 14.7 h.

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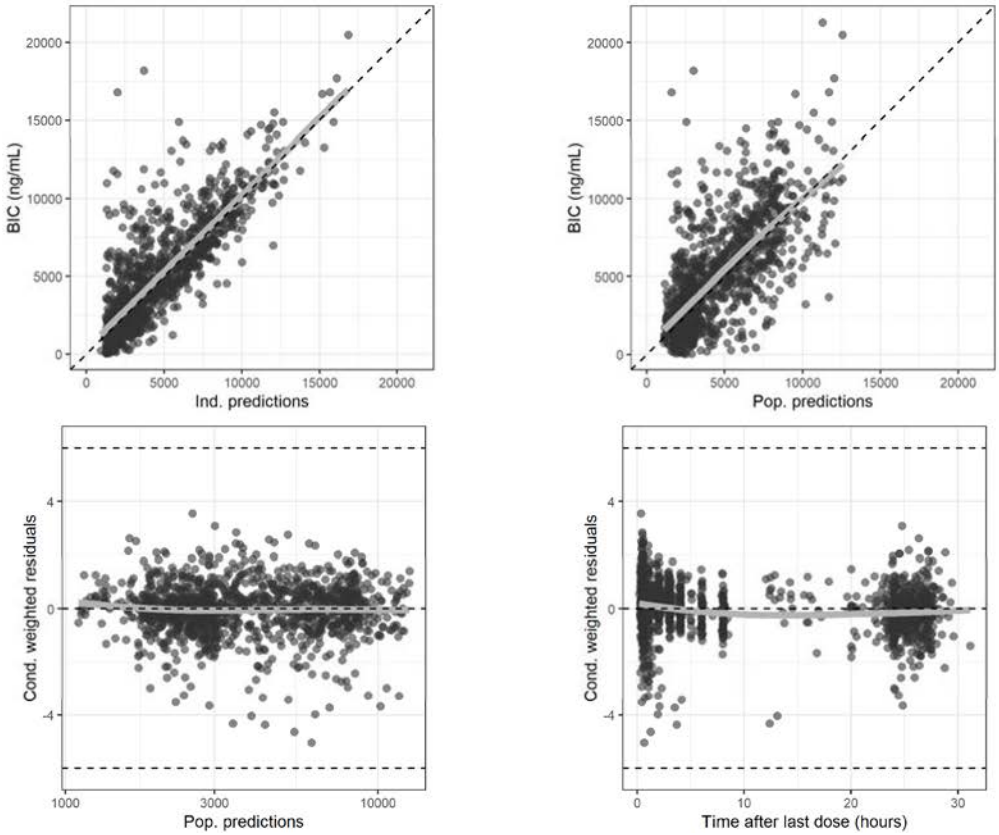
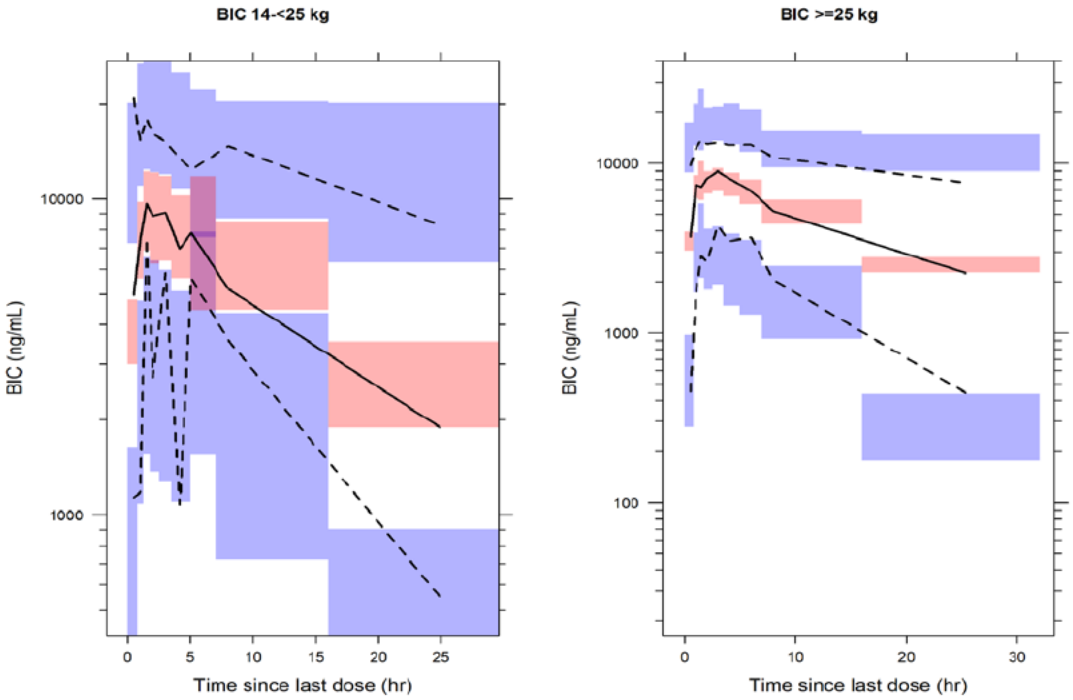
Figure 6 Goodness-of-Fit (GOF) plots for the final BIC model for all pediatric subjects from Study GS-US-380-1474



Source: Applicant's BIC peds PopPK report. Figure 4. Page 29.

Figure 7 pcVPC of the final PopPK model stratified by WT (14 to <25 kg and >=25 kg)



Source: Applicant's BIC peds PopPK report. Figure 5. Page 30.

The effect of WT was the most influential covariate, with a maximum percentage change in BIC exposures ranging from −44% to +100% (relative to the median exposures) for subjects with 67.9 kg and 15.2 kg. The covariate effect of Asian race resulted in approximately 37% increase in BIC exposures in pediatric subjects. Proton-pump inhibitor administration had minimal effect on exposures with approximately 5% change.

Table 8 summarizes the mean (CV%) for model-predicted BIC plasma exposures for Study GS-S-380-1474 by body weight groups and referenced adult exposures.

Table 8 PopPK derived Bictegravir Plasma PK Parameter Estimates pediatric patients ≥ 2 Years of Age Weighing ≥ 14 to < 25 kg (Cohort 3), 25 to <35 kg, and >35 kg and Adults

	Pediatric Patients (Study GS-US-380-1474)			Adults [a]	%GLSM Ratio (90%CI)
	≥ 35 kg	25 to < 35 kg	14 to < 25 kg		Cohort 3 vs. Adults
	N = 60	N = 40	N = 22	N=1193	-
AUC_{tau} (h•ng/mL)	101018 (34.7)	135168 (27.9)	126087 (42.4)	102001.0 (26.9)	118.19 (102.15, 136.76)
C_{max} (ng/mL)	6453 (38)	9255.6 (27.1)	9147 (44.8)	6145.8 (22.9)	138.60 (117.61, 163.34)
C_{tau} (ng/mL)	2411.9 (33.2)	2889.9 (32.5)	2434.6 (40.1)	2609.9 (35.2)	93.34 (82.58, 105.51)

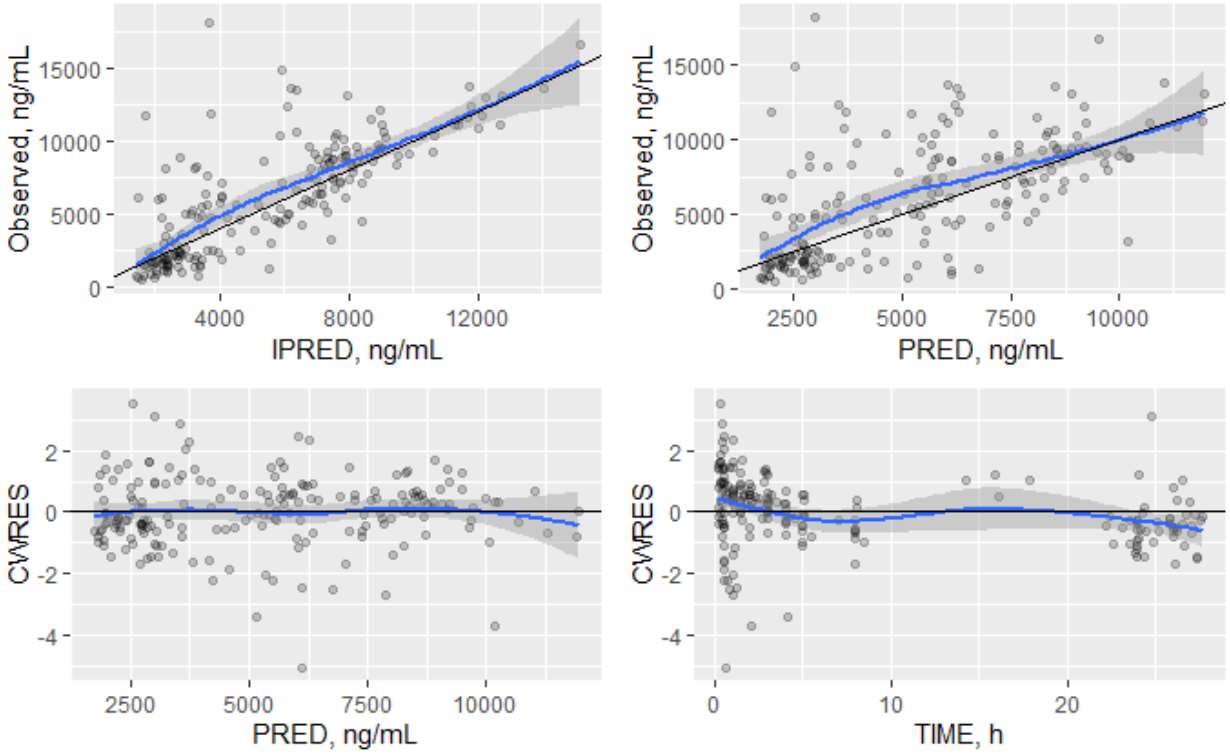
[a] PopPK derived exposures for adults were from B/F/TAF-treated adults in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878

Source: Adapted from Applicant's Table 2 (page 20) of Summary of Clinical Pharmacology Studies, and Table 23 (page 38), BIC peds PopPK report.

Reviewer comments:

The final PopPK model of BIC is acceptable in describing the observed BIC PK in pediatric patients aged 3 years and older and with body weight >14.1 kg. Parameters were estimated with acceptable precision with %RSE for fixed-effect parameters generally < 30%. Parameter estimates are similar to those in the previously submitted BIC model developed based on data from Cohort 1 and 2 (Refer to Clinical Pharmacology Review for NDA210251-S5). The GOF plots (Figure 6) show agreement between the predicted concentrations and observed concentrations in all three cohorts. The GOF plots in subgroup of body weight 14 to <25kg (Figure 8) did not show any unacceptable bias. The magnitude of ETA shrinkage of the final PopPK model was small (<15%) for CL/F, and Vc/F. Applicant's pcVPC plots stratified by weight group show that the final PopPK model generally captures the central tendency and the variability of the plasma concentrations for both body weight categories. The final PoPK model is acceptable to estimate BIC exposures at steady state for Cohort 3 for the comparison with adult exposures.

Figure 8 GOF plots in the subgroup with body weight (14 to <25 kg)



Source: Reviewer's figure based on the Applicant's BIC PopPK model.

The weight effect was included in the model with allometric scaling with theoretical exponents on CL and V. While ETA-covariate plots (eta for CL or Vc – body weight) show no obvious trend in body weight range < 60 kg, but there is a notable bias in the body weight range (i.e., >60 kg) (Figure 9). For the purpose of describing PK in the population of interest (14 to <25kg), the

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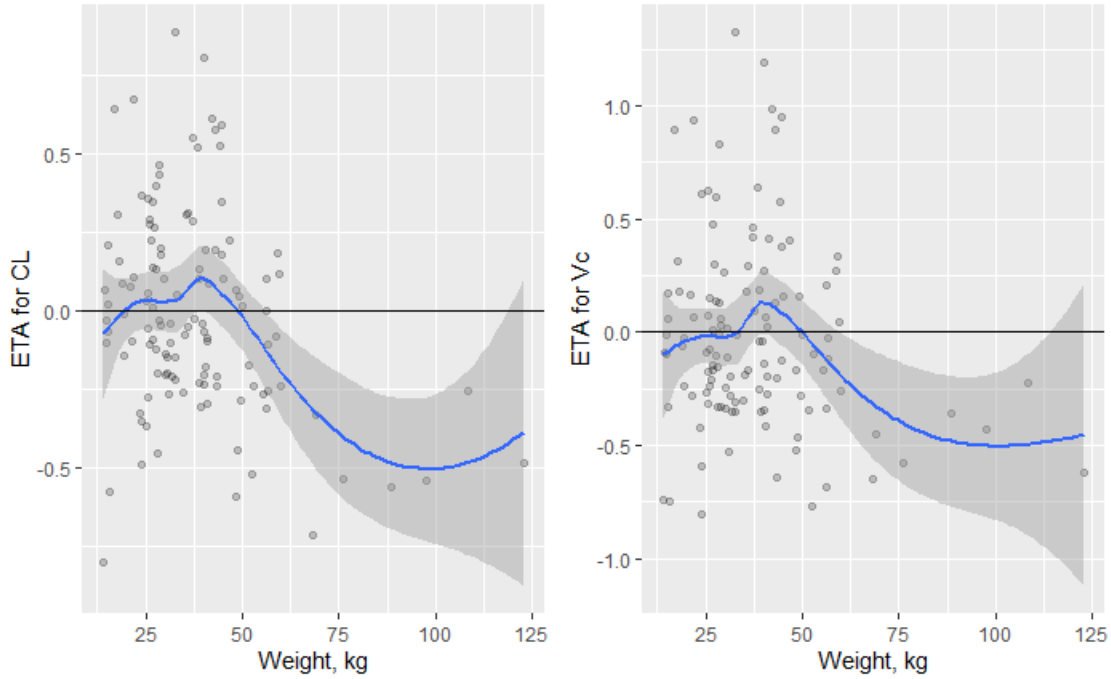
covariate model is acceptable. However, the covariate model for weight effect should be re-evaluated if this model is used for any simulation for patients with higher body weight (i.e., > 60 kg) as it is likely overestimating CL and Vc.

Figure 9 ETA – body weight relationship



Source: Reviewer's figure based on the Applicant's BIC PopPK model.

6.3 Tenofovir Alafenamide (TAF) and Tenofovir (TFV)

Reviewer's note: *Pediatric PopPK models for TAF and TFV (Report# QP-2018-1027 TAF TFV HIV Pediatric Pop PK) were previously submitted to support the previous submission NDA210251-S5 (SD234) for one tablet (B/F/TAF; 50/200/25 mg) taken once daily with or without food in patients with body weight at least 25 kg. Division of Pharmacometrics has reviewed these models and determined deemed acceptable. In the current submission with the addition of pediatric PK data, there have been substantial modifications in structural models for TAF and TFV models from the previously submitted models.*

The previous PopPK model for TAF described the plasma concentrations of TAF by a 2-compartment model with the M3 method, zero-order input with first-order absorption and linear elimination; IIV was included on CL/F, Vc/F, ka, and D1; covariance was included on CL/F and Vc/F, and ka and D1; a proportional error model (for log-transformed data) was used to describe residual variability (RV). With current submission, the Applicant reported that the previous TAF model was subject to reproducibility and robustness issues: terminated minimizations, large condition number, very high correlations between parameters, and high sensitivity to initial estimates with large fluctuation in the OFV. Therefore, in the attempt of improving model stability, the Applicant incorporated following key modifications in TAF model:

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1) Simplification of the absorption model to a first-order process
2) Exclusion of all PK samples beyond 5.5 hours postdose.
3) Inclusion of IIV on the proportional error
4) Inclusion of PK boosting impacts within the base model

The previous PopPK model for TFV (a major metabolite of TAF) described TFV plasma concentrations by a 2-compartment model, zero-order input with first order absorption, linear elimination, IIV on CL/F, Vc/F and D1, covariance on CL/F & Vc/F, and a proportional error model (for log-transformed data). With current submission, the Applicant performed sequential modeling for TAF-TFV, using the posthoc individual PK parameters from the TAF model as the input to characterize TFV PK, instead of a standalone TFV model.

Applicant's PopPK analysis for TAF and TFV

Data: Four Phase 2/3 studies were included in this analysis to evaluate the PK and safety of TAF and TFV (Table 9). The analysis population was primarily black (75.1%), with a median (range) age of 12 (3, 17) years and WT of 38.0 (14.1, 123) kg, and 57.6% being female subjects.

- TAF model: A total of 1432 samples (of which 1364 were BLQ samples) were marked for exclusion because they were collected later than 5.5 hours postdose. In total, 1709 samples from 337 subjects were used for TAF model development.
- TAF-TFV model: A total of 14 samples were marked for exclusion, 10 BLQ samples and 4 outliers with |CWRES| > 6. In total, 3176 samples from 337 subjects were used for TFV model development

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Table 9 Clinical studies included in the PPK analyses for TAF and TFV

Study	Study Design/Population	Treatment	Sampling (Intensive/Sparse)
GS-US-292-0106	A Phase 2/3, Open-Label Study of the Pharmacokinetics (PK), Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1–Infected, Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children	Cohorts 1 and 2 (adolescents and children [6 to < 18 years of age, weighing ≥ 25 kg]): E/C/F/TAF 150/150/200/10 mg fixed-dose combination (FDC) Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): E/C/F/TAF 90/90/120/6 mg FDC	Intensive + Sparse
GS-US-292-1515	A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1–Infected, Virologically Suppressed Adolescents	E/C/F/TAF 150/150/200/10 mg FDC	Sparse
GS-US-311-1269	A Phase 2/3, Open-Label, Multicohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1–Infected Children and Virologically Suppressed Adolescents on a 2-Nucleoside Reverse Transcriptase Inhibitor (NRTI)-Containing Regimen	Cohort 1 (adolescents 12 to < 18 years of age, weighing ≥ 35 kg): F/TAF 200/25 mg or 200/10 mg FDC Cohort 2 Group 1 (children 6 to < 12 years of age, weighing ≥ 25 kg): F/TAF 200/25 mg Cohort 2 Group 2 (children 2 to < 12 years of age, weighing ≥ 17 to < 25 kg): F/TAF 120/15 mg	Intensive + Sparse
GS-US-380-1474	A Phase 2/3, Open-Label Study of the PK, Safety, and Antiviral Activity of the GS-9883/F/TAF) FDC in HIV-1–Infected, Virologically Suppressed Adolescents and Children	Cohorts 1 and 2 (adolescents [12 to < 18 years of age] and children [6 to < 12 years of age]): B/F/TAF 50/200/25 mg FDC Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): B/F/TAF 30/120/15 mg FDC	Intensive + Sparse

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetic(s).

Source: Applicant's PPK report for TAF/TFV. Table 1. Page 23.

Table 10 Summary Statistics of Continuous Covariates Used in TAF PopPK Analysis

Covariate	Statistics	GS-US-292-0106 (N = 129)	GS-US-292-1515 (N = 50)	GS-US-311-1269 (N = 36)	GS-US-380-1474 (N = 122)	Total (N = 337)
Age (years)	Mean (SD)	10.9 (3.72)	14.8 (1.62)	13.1 (2.35)	10.8 (3.76)	11.7 (3.68)
	Median [Min, Max]	11.0 [3.00, 17.0]	15.0 [12.0, 17.0]	13.0 [8.00, 17.0]	11.0 [3.00, 17.0]	12.0 [3.00, 17.0]
WT (kg)	Mean (SD)	36.9 (15.8)	54.1 (13.9)	43.1 (9.19)	37.6 (18.0)	40.4 (16.9)
	Median [Min, Max]	33.1 [14.6, 88.8]	52.2 [35.1, 101]	43.4 [22.0, 62.4]	34.0 [14.1, 123]	38.0 [14.1, 123]
BMI (kg/m^2)	Mean (SD)	17.9 (3.44)	21.3 (4.92)	19.1 (2.33)	18.6 (5.04)	18.8 (4.36)
	Median [Min, Max]	17.4 [12.4, 31.8]	19.8 [15.5, 38.6]	18.7 [14.0, 25.1]	17.7 [12.6, 45.7]	17.9 [12.4, 45.7]
BSA (m^2)	Mean (SD)	1.19 (0.326)	1.54 (0.211)	1.33 (0.194)	1.19 (0.333)	1.25 (0.327)
	Median [Min, Max]	1.12 [0.640, 2.03]	1.52 [1.19, 2.13]	1.35 [0.880, 1.71]	1.14 [0.590, 2.37]	1.23 [0.590, 2.37]
BCL_{CRSW} (mL/min/ 1.73 m^2)	Mean (SD)	154 (28.4)	160 (26.2)	162 (31.4)	156 (29.0)	156 (28.7)
	Median [Min, Max]	150 [98.6, 284]	158 [102, 223]	157 [108, 236]	151 [89.0, 259]	153 [89.0, 284]

BMI = body mass index; BSA = body surface area; BCL_{CRSW} = baseline creatinine clearance derived by Schwartz equation; N = number of subjects; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; WT = baseline body weight

Source: Applicant's PPK report for TAF/TFV. Table 7. Page 36.

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Table 11 Summary Statistics of Categorical Covariates Used in TAF PopPK Analysis

Covariate	Category	GS-US-292-0106 N (%)	GS-US-292-1515 N (%)	GS-US-311-1269 N (%)	GS-US-380-1474 N (%)	Total N (%)
Sex	Male	54 (41.9%)	18 (36.0%)	19 (52.8%)	52 (42.6%)	143 (42.4%)
	Female	75 (58.1%)	32 (64.0%)	17 (47.2%)	70 (57.4%)	194 (57.6%)
Race	White	2 (1.6%)	1 (2.0%)	3 (8.3%)	3 (2.5%)	9 (2.7%)
	Black	105 (81.4%)	49 (98.0%)	15 (41.7%)	84 (68.9%)	253 (75.1%)
	Asian	22 (17.1%)	0 (0%)	1 (2.8%)	29 (23.8%)	52 (15.4%)
	Other	0 (0%)	0 (0%)	17 (47.2%)	6 (4.9%)	23 (6.8%)
P-gp inhibitors	No	97 (75.2%)	50 (100%)	34 (94.4%)	109 (89.3%)	290 (86.1%)
	Yes	32 (24.8%)	0 (0%)	2 (5.6%)	13 (10.7%)	47 (13.9%)
Booster groups	Unboosted	0 (0%)	0 (0%)	14 (38.9%)	122 (100%)	136 (40.4%)
	COBI	129 (100%)	50 (100%)	0 (0%)	0 (0%)	179 (53.1%)
	LPV/RTV	0 (0%)	0 (0%)	22 (61.1%)	0 (0%)	22 (6.5%)
PPIs	No	126 (97.7%)	50 (100%)	35 (97.2%)	120 (98.4%)	331 (98.2%)
	Yes	3 (2.3%)	0 (0%)	1 (2.8%)	2 (1.6%)	6 (1.8%)
H2RAs	No	128 (99.2%)	49 (98.0%)	35 (97.2%)	121 (99.2%)	333 (98.8%)

COBI = cobicistat; H2RA = histamine 2 receptor antagonist; LPV = lopinavir; N = number of subjects; P-gp = P-glycoprotein; PopPK = population pharmacokinetic; PPI = proton-pump inhibitor; RTV = ritonavir; TAF = tenofovir alafenamide

Source: Applicant's PPK report for TAF/TFV. Table 8. Page 37.

Reviewer's note: *The four pediatric studies included in the TAF/TFV model developments used different FDC products containing TAF. This review is mainly focused on the PopPK analysis characterizing PK for TAF/TFV when administered as BIKTARVY (B/FTC/TAF FDC).*

6.2.1 Tenofovir Alafenamide (TAF)

Base model: The final base model was a 1-compartment structural model with first-order absorption and first-order elimination. The base model included weight effects on CL/F and Vc/F using fixed allometric exponents of 0.75 and 1. In addition, COBI was found to affect F1. IIV was included on ka. Introducing IIV on additional PK parameters (ie, CL/F and Vc/F) resulted in large instability with terminated runs and 0 gradients across multiple parameters. A combined error model was used to characterize residual variability, with the additive error term fixed to half of the lower limit of quantitation (0.5 ng/mL) and the inclusion of IIV on the proportional error term.

TAF model #1 (run078_tv): The initially submitted final TAF model was a 1-compartment model with sequential zero- first-order absorption and first-order elimination. Effects of WT on CL/F and Vc/F were included using fixed allometric exponents of 0.75 and 1, respectively. COBI was found to affect F1 (163.6% increase), and TAF Vc/F was found to be lower in Asian subjects (78.8% reduction). IIV was included on D1. A combined error model was used to

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characterize residual variability, with the inclusion of IIV on the proportional error term. Parameter estimates are presented in Table 12 and the standard GOF plots are presented in Figure 10. Shrinkage estimates of the final TAF PPK model was 23.2% and 0.2% for ETAs for residual proportional error, and D1. The pcVPC simulations stratified by booster groups are presented in Figure 11.

Table 12 Parameter Estimates for Initially Submitted TAF PopPK model (run078_tv)

Parameter	Parameter Description	Population Estimate	Change from Typical (%)	IIV (%)
$\exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)	130	--	--
$\exp(\theta_1) \times ((\frac{WT}{38})^{0.75})$	Influence of WT on CL/F, 5th %ile of WT	71	-45.3	--
	Influence of WT on CL/F, 95th %ile of WT	201	54.7	--
$\exp(\theta_2)$	Apparent central volume of distribution (non-Asian), V_c/F (L)	24.6	--	--
$\exp(\theta_1) \times ((\frac{WT}{38})^{1})$	Influence of WT on V_c/F, 5th %ile of WT	11	-55.3	--
	Influence of WT on V_c/F, 95th %ile of WT	44	78.9	--
$\exp(\theta_2) \times (1+\theta_8)$	Apparent central volume of distribution (Asian), V_c/F (L)	5	-78.8	--
$\exp(\theta_3)$	First order absorption rate constant, k_a (1/h)	1.7	--	--
$\exp(\theta_7)$	Duration of zero-order absorption, D1 (h)	1.5	--	108
$1 \times (1+\theta_6)$	COBI-boosted relative bioavailability (F1)	2.6	163.6	--
$\sqrt{\theta_4}$	Residual proportional error (%)	126	--	60
θ_5	Residual additive	0.5 [FIXED]	--	--

Source: Applicant's PopPK report for TAF/TFV. Table 10. Page 45.

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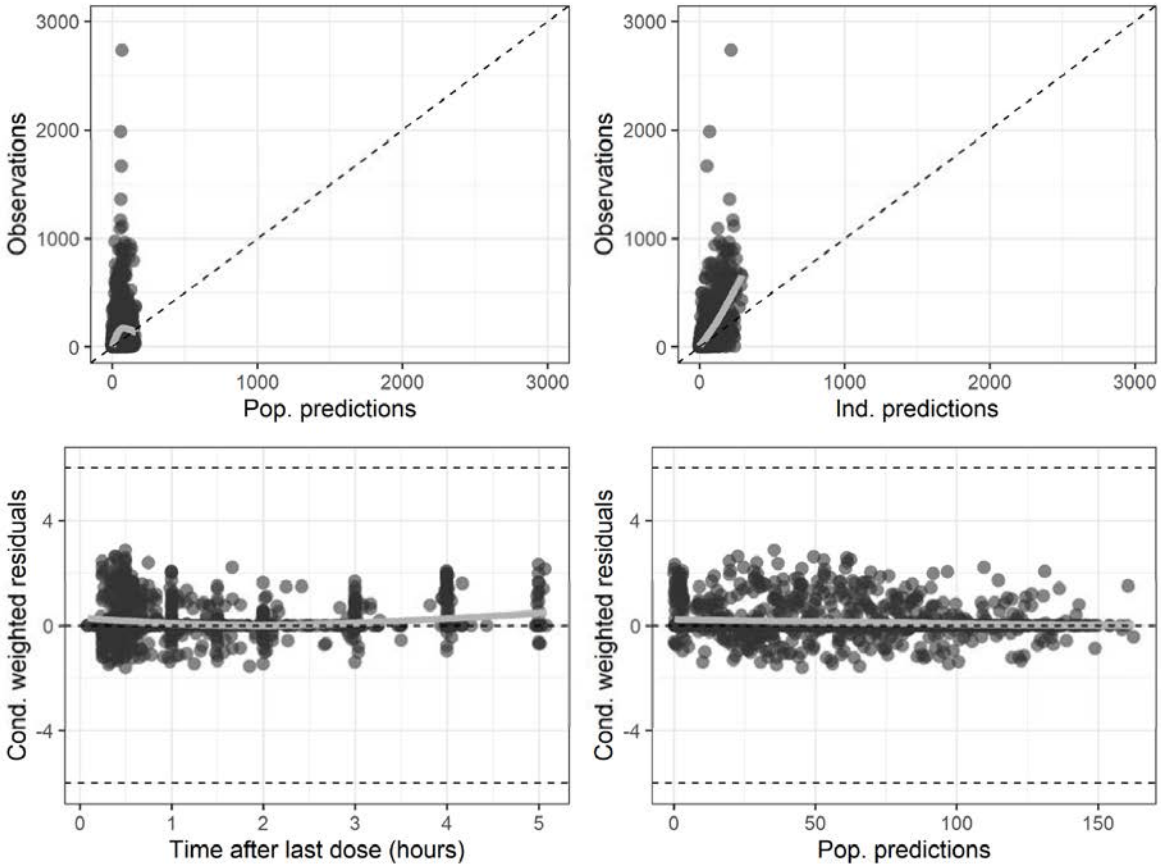
Figure 10 GOF plots for TAF model (run078_tv) for all pediatric subjects from PopPK analysis set



Source: Applicant's PopPK report for TAF/TFV. Figure 31. Page 149.

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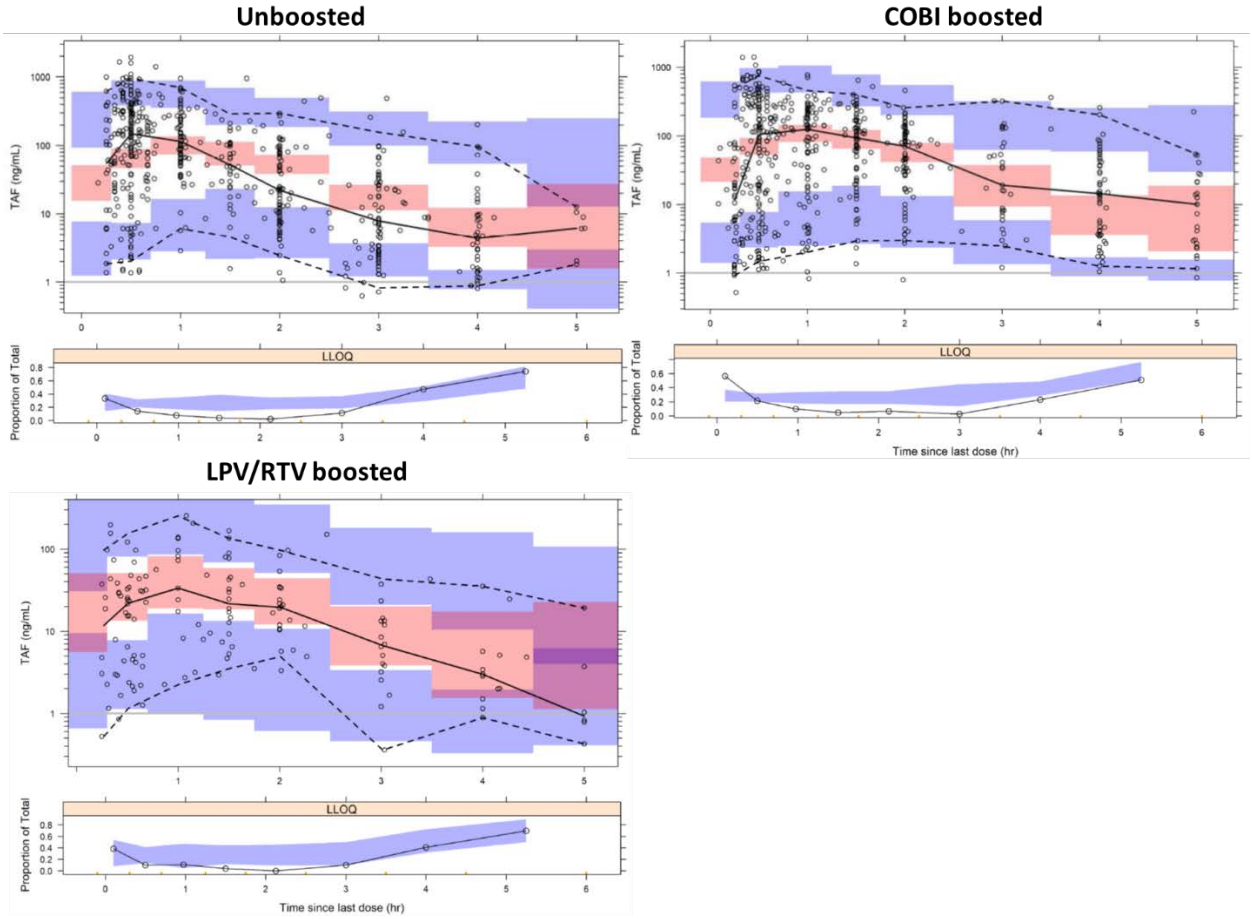
Figure 11 pcVPC of TAF PopPK Model (run078_tv) Stratified by Boost groups



Source: Applicant's PopPK report for TAF/TFV. Figure 10. Page 49.

***Reviewer's comment**: The PopPK model (run078_tv) for TAF does not adequately describe the observed plasma concentrations of TAF in pediatric patients enrolled in Study GS-US-380-1474. The Applicant's pcVPC plots stratified by booster groups show that the model underpredict the TAF concentrations in absorption phase and overpredict after Tmax. This trend is pronounced in the "unboosted" group which primarily includes the data from Study GS-US-380-1474. Also, model-derived exposures metrics were significantly deviated from those observed in intense PK sampling. It is noted that the Applicant made extensive attempts to improve model stability during model development, however, the reviewer could not reproduce the parameter estimation due to consistent rounding error. Per the Agency's request (Information Request [IR] dated 7/2/2021), the Applicant provided the updated model (run091) to address the reproducibility and the model misspecification (Response to IR received on 8/7/2021).*

TAF model #2 (run091): In the updated TAF model, the Applicant included boosting agent effects (COBI or LPV/RTV) on the D1 parameter in the submitted TAF model (run078_tv). The impact of the booster effect on D1 was estimated as 259%. Parameter estimates from the updated TAF model (run091) were similar to initial parameter estimates from the initially submitted model. With the updated model, the Applicant reported similar challenges on model reproducibility; the large proportion of BLQ samples in the original dataset (60%) as well as the

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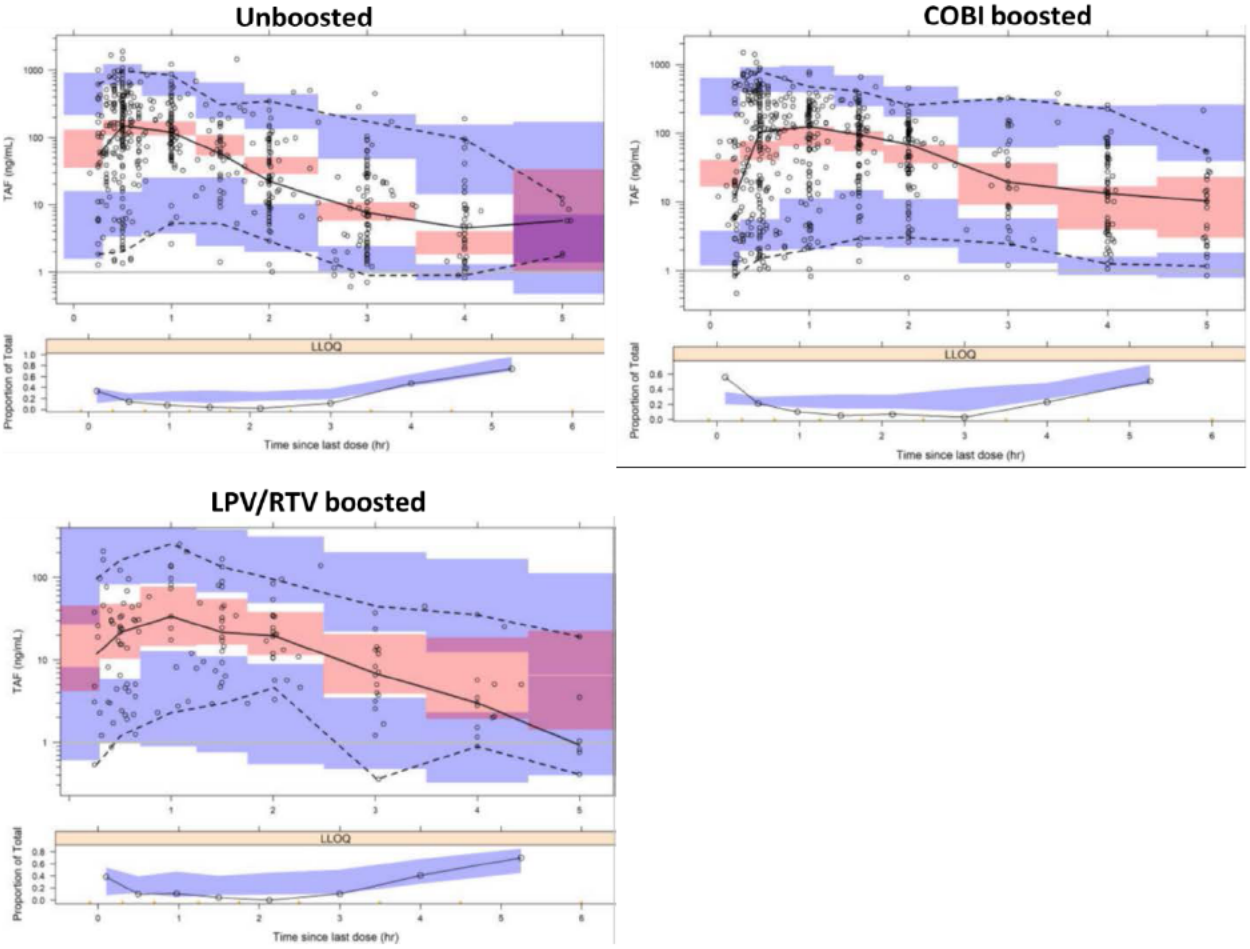
heterogeneous TAF absorption are thought to be key factors influencing model stability and parameter identifiability.

Figure 12 pcVPC of updated TAF PopPK model (run091) stratified by boost groups



Source: Applicant's response to Clinical Pharmacology IR.

Reviewer's Assessment:

The updated TAF model (run091) reasonably describes the time-TAF concentration profiles capturing Tmax and the trend of terminal elimination for the unboosted group (Figure 12). However, the similar underprediction at Tmax is still observed, and the estimation steps are consistently terminated due to the rounding error. (b) (4) [redacted]

To examine the reliability of the parameter estimates when administered as BIKTARVY, the reviewer conducted a sensitivity analysis based on the "unboosted" group only (the data from 122 subjects in Study GS-US-380-1474 and 14 subjects from Study GS-US-380-1269) by fitting the TAF model which has the same structural model as run091 but incorporating IIV estimation for CL/F, and V/F. In general, individual PK estimates were similar for CL/F and D1 between the sensitivity run vs. the updated model (run091), however a sensitivity run produced higher

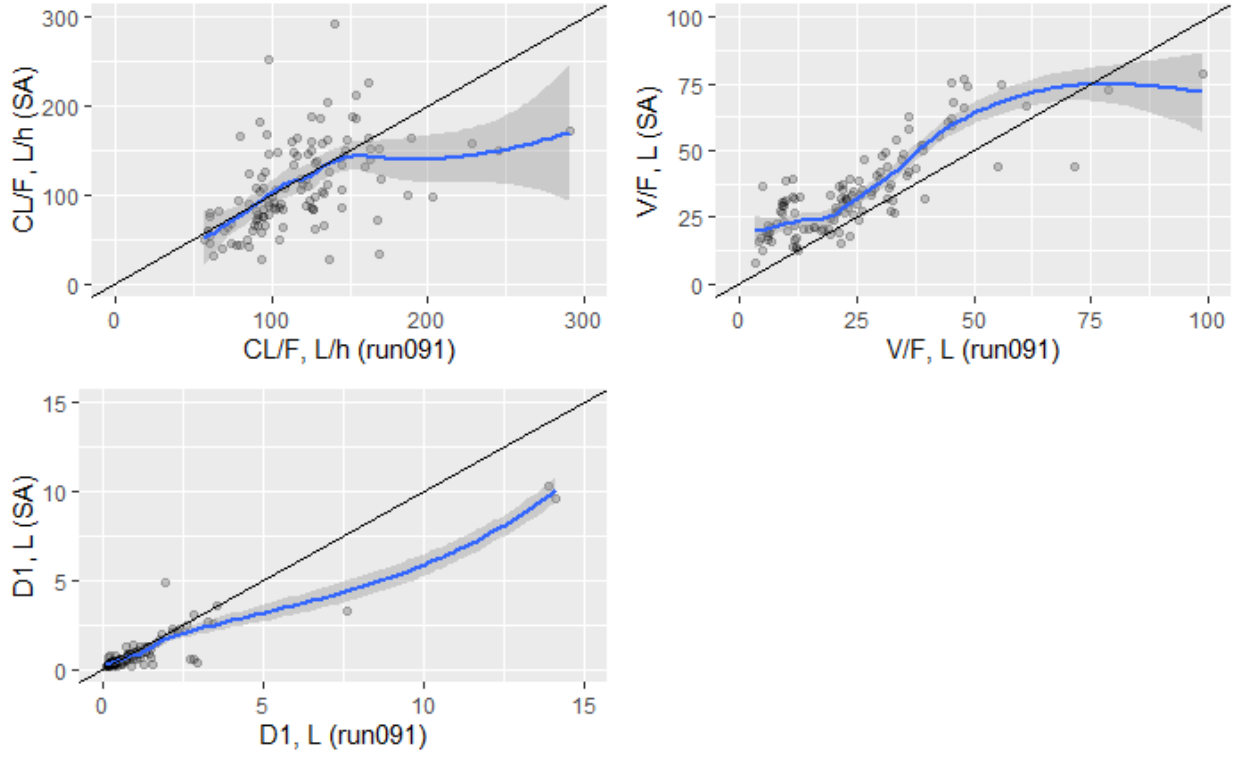
Vc/F (Figure 13). The impact of these different parameters on TFV PK characterization is further discussed in the next section discussing TFV PopPK analysis.

Table 13 Comparison of parameter estimates from TAF models with Sensitivity Analysis

Parameter Description	***[a]Updated TAF model (run91)***	***Reviewer's sensitivity model (unboosted only)***
CL/F (L/h)	*121*	*103*
Vc/F (L)	*30.6*	*40*
ka (1/h)	*1.77*	*2.35*
COBI effect on F1	*1.49*	*-*
Duration of zero-order absorption, D1 (h)	*0.459*	*0.471*
COBI/LPV/RTV effect on D1	*2.59*	*-*
Asian effect on Vc/F	*-0.719*	*-0.342*
Residual proportional error (%)	*120*	*103*
Residual additive	*0.5 [FIXED]*	*0.5 [FIXED]*
IIV of CL/F (%)	*Not estimated*	*57*
IIV of Vc/F (%)	*Not estimated*	*41*
IIV of D1 (%)	*137*	*176*
IIV of proportional error (%)	*62*	*0.15*

Source: Reviewer's table. [a]Applicant's response to Clinical Pharmacology IR.

Figure 13 Comparison of PK parameters between the updated model (run091) and the sensitivity run (SA)



Source: Reviewer's plot.

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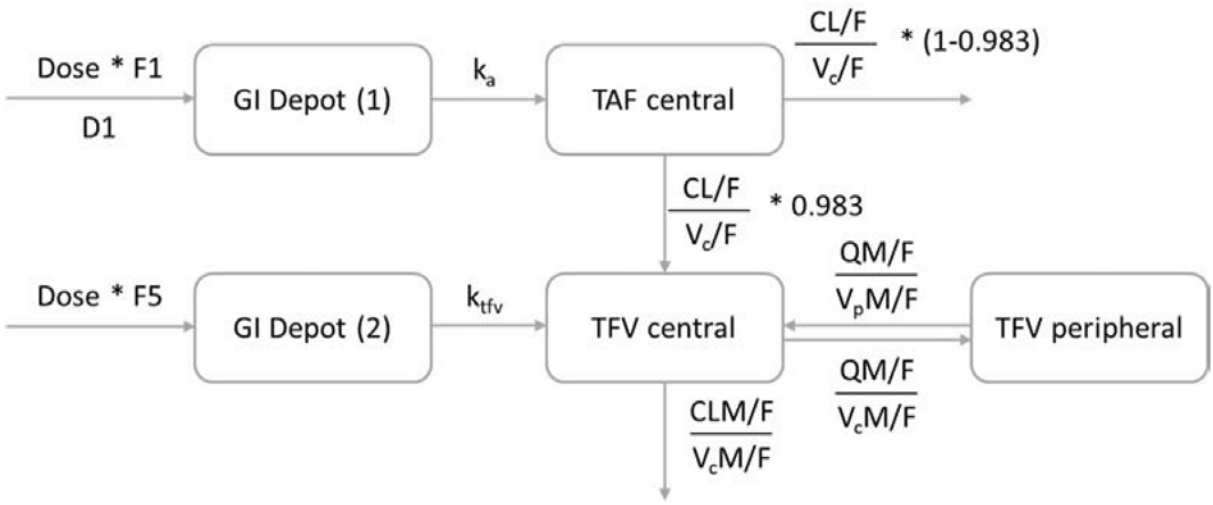
6.2.2 Tenofovir (TFV)

Base model: Posthoc PK parameters of the final TAF PopPK model (Run078_tv) were used as input for the sequential TAF-TFV PopPK model. A metabolic conversion rate of 98.3% was assumed in the formation of TFV from TAF central compartment. The 2-compartment model was used to describe TFV disposition. Body weight effects were included on the apparent oral clearance of TFV (CLM/F), apparent intercompartmental clearance of TFV (QM/F), apparent central volume of distribution of TFV (VcM/F), and apparent peripheral volume of distribution of TFV (VpM/F) using fixed allometric exponents of 0.75 and 1, for clearances and volumes of distribution. The Applicant reports a clear systematic underprediction of LPV/RTV-boosted TFV data. To address this misspecification, a parallel absorption compartment with a first-order process from TAF dose directly to systemic TFV was incorporated to describe the TFV data in the presence of the LPV/RTV booster. IIV was included on CLM/F, QM/F, VcM/F, and VpM/F; and a combined proportional and additive error model was used to characterize RV.

Figure 14 PopPK model diagram for sequential TAF-TFV Analysis



Source: Applicant's PopPK report for TAF/TFV. Figure 10. Page 49.

Covariate analysis: In addition to weight effect and booster effects on F included the base model the following covariates were further evaluated in the stepwise covariate analysis:

- CLM/F: age, sex, race, baseline creatinine clearance derived by Schwartz equation (BLCLCRSW), and P-gp inhibitors co-medication
- VcM/F: age, sex, and race

The only significant parameter-covariate relationship identified during the stepwise covariate analysis was BCLCRSW on CLM/F. The effect was retained after the backward deletion step and therefore accepted in the final model.

Final TFV model #1 (run028): A sequential 1-compartment TAF model (Run078_tv) and 2-compartment TFV model with first-order elimination was used to describe the TFV pediatric data. A parallel absorption compartment with first-order process was introduced in the model to describe TFV data in the presence of the LPV/RTV booster. A combined proportional and additive error model was used to characterize RV. The final parameter estimates with the final

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PopPK model for TFV are presented in Table 14. The standard GOF plots and pcVPC plots are presented in Figure 10, and Figure 16. Shrinkage estimates for IIV for CLM/F, QM/F, VcM/F, and VpM/F were 7.3%, 33.7%, 74.3%, and 60.7%. The terminal $t_{1/2}$ was calculated as 41.9 h.

Table 14 Parameters for Final TFV PopPK Model (run028)

Parameter	Parameter Description	Population Estimate	Change from Typical (%)	IIV (%)
$\exp(\theta_1)$	Apparent oral clearance, CLM/F (L/h)	124	--	23
$\exp(\theta_1) \times ((\frac{WT}{38})^{0.75})$	Influence of WT on CLM/F, 5th %ile of WT	68	-45.3	--
	Influence of WT on CLM/F, 95th %ile of WT	191	54.7	--
$\exp(\theta_1) \times ((\frac{CLCRSW}{153})^{\theta_9})$	Influence of BCL_{CRSW} on CLM/F, 5th %ile of BCL_{CRSW}	104	-15.8	--
	Influence of BCL_{CRSW} on CLM/F, 95th %ile of BCL_{CRSW}	147	19.3	--
$\exp(\theta_2)$	Apparent central volume of distribution, V_cM/F (L)	1750	--	116
$\exp(\theta_1) \times ((\frac{WT}{38})^{1})$	Influence of WT on V_cM/F, 5th %ile of WT	782	-55.3	--
	Influence of WT on V_cM/F, 95th %ile of WT	3126	78.9	--
$\exp(\theta_3)$	Apparent peripheral volume of distribution, V_pM/F (L)	5520	--	24
$\exp(\theta_3) \times ((\frac{WT}{38})^{1})$	Influence of WT on V_pM/F, 5th %ile of WT	2468	-55.3	--
	Influence of WT on V_pM/F, 95th %ile of WT	9871	78.9	--
$\exp(\theta_4)$	Apparent intercompartmental clearance, QM/F (L)	2300	--	55
$\exp(\theta_3) \times ((\frac{WT}{38})^{0.75})$	Influence of WT on QM/F, 5th %ile of WT	1259	-45.3	--
	Influence of WT on QM/F, 95th %ile of WT	3560	54.7	--
$\exp(\theta_8)$	TFV first order absorption rate constant from second depot compartment, k_{TFV} (1/h)	0.151	--	--
$1 \times (1+ \theta_7)$	LPV/RTV-boosted relative bioavailability	3.1	209.5	--
$\sqrt{\theta_5}$	Residual proportional error (%)	45	--	--
θ_6	Residual additive	1.2	--	--

Source: Applicant's PopPK report for TAF-TFV. Table 33 on page 66. The 5th and 95th percentiles of WT are 17 and 68 kg; the 5th and 95th percentiles of BCL_{CRSW} are 114 and 207 mL/min/1.73 m^2.

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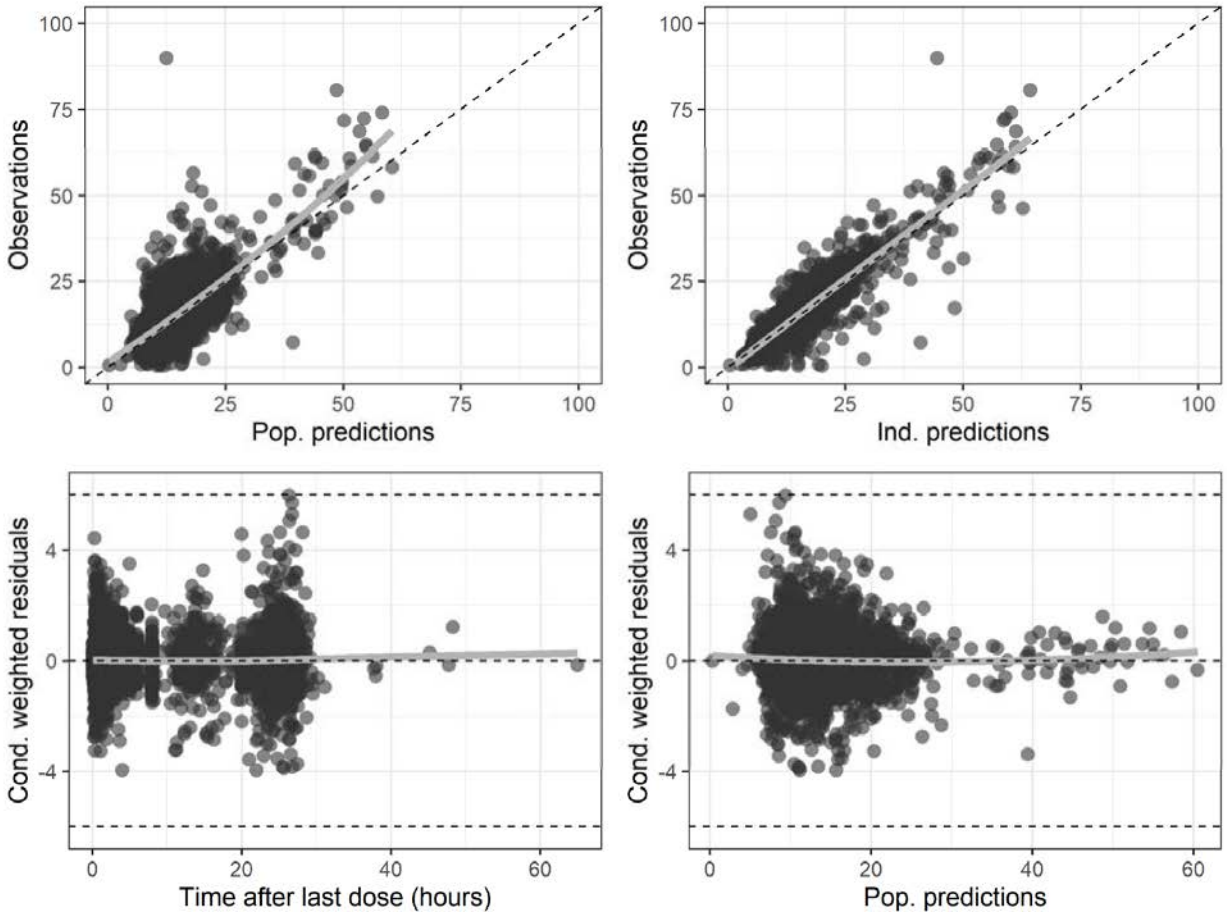
Figure 15 Standard Goodness-of-Fit Plots for the Final TFV PopPK Model for Pediatric Subjects



Source: Applicant's PopPK report for TAF-TFV. Figure 14 on page 67.

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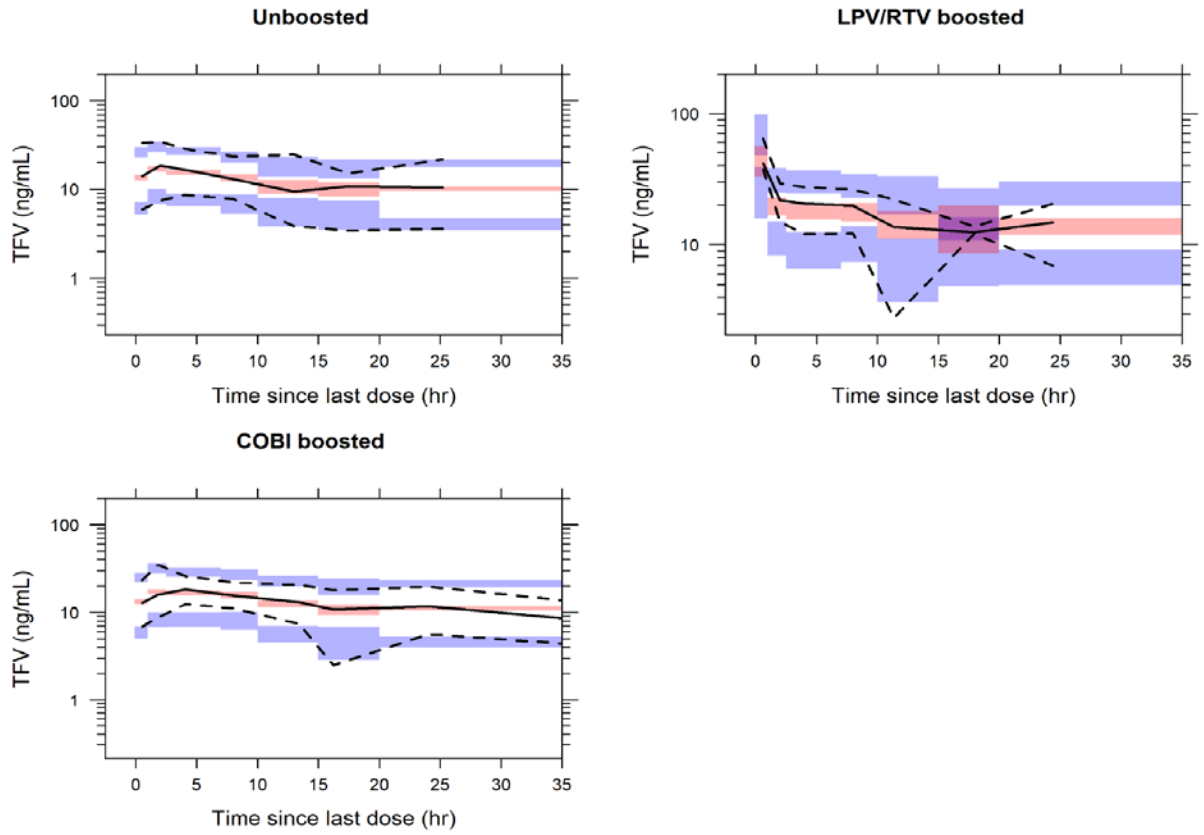
Figure 16 pcVPC of TFV PopPK model (run091) stratified by boost groups



Source: Applicant's PopPK report for TAF-TFV. Figure 15 on page 68.

The TFV exposures were inversely correlated with WT, with a percent change in TFV exposures ranging from −37.4% to +89.9% (relative to the median exposures) for subjects with 68 kg and 17 kg body weight. LPV/RTV and COBI were the most influential covariates with an increase in TFV exposures of +231 and +164%, respectively. The effect of BCLCRSW was a minimally influential with a percent change in TFV exposures ranging from −18.4% to +20.1% (relative to the median exposures) for subjects with 207 mg/mL/min/1.73 m^2 (95^{th} percentile) and 114 mg/mL/min/1.73 m^2 (5^{th} percentile).

Updated TFV model #2 (run032): As TAF model (run091) was updated from the originally submitted model (run078_tv), the Applicant re-estimated TFV model (run032) with the updated individual PK parameters from the TAF model. The updated TAF model had a marginal impact on the subsequent TAF-TFV model, with minimal changes in the parameter estimates and almost identical GOF plots and pcVPC plots.

Reviewer's comments:
Applicant's characterizing PK of TAF and TFV simultaneously using the sequential model is a physiologically feasible approach. Although the Applicant's TAF model (run091) caused terminated minimization due to rounding error, this model is considered adequate to inform TFV PopPK analysis. To examine a potential impact of TAF model stability issue in characterizing TFV PK following administration of unboosted TAF (BIKTARVY), the reviewer refitted the TFV

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model with the different set of individual TAF PK parameters estimated by the reviewer's sensitivity run for TAF. The model parameters for TFV are generally consistent between the Applicant's and the reviewer's (Table 15). The individual PK parameters for TFV (CLM/F, QM/F, VcM/F, and VpM/F) derived from these runs are nearly identical. TAF is rapidly absorbed and metabolized to TFV (half-life of 0.5 hour). Assuming fixed conversion rate of 98%, the overall exposure of TAF, which is reflected as CL/F and relative BA, are thought to be the determinant factors for TFV PK. The underprediction in the absorption phase of the TAF model is thought to be minimally impact on characterization TFV PK.

Taken together, Applicant's PopPK analysis for TFV is acceptable to derive individual exposure metrics for pediatric patients weighing >14 kg receiving BIKTARVY. The parameters were estimated with acceptable precision (%RSE of < 25%) for most parameters. The GOF plots by all data and stratified by booster group and age group show a good agreement between the predicted and the observed data without any unacceptable bias in residuals over time and across the predicted concentration range. The pcVPC plots stratified by booster group generally capture the central tendency and the observed variability of the observed TFV concentrations. Shrinkage is low for IIV of CLM/F (<10%) and modest for QM/F, VcM/F, and VpM/F.

The relevant covariates for TFV when TAF is administered as BIKTARVY are WT on the parameters for clearance and volume of distributions, BCLCRSW on CLM/F. The reviewer's examination of ETA-covariate plots did not identify unacceptable bias. In this review, the covariate models for booster effect on k_{TAF}, LPV/RTV effect on relative bioavailability are not discussed in detail, as these are not relevant to BIKTARVY.

Table 15 Comparison of Parameter estimates for TAF-TFV sequential model with different TAF models

Parameter Description	[a]***Updated TFV model (run032)***	[b]***Reviewer's TFV run (unboosted only)***
Model used for TAF	*Updated TAF model (run091)*	*Reviewer's sensitivity TAF model (run179)*
Apparent oral clearance, CLM/F (L/h)	*120*	*117*
Apparent central volume of distribution, VcM/F (L)	*1830*	*1525*
Apparent intercompartmental clearance, QM/F (L/h)	*2320*	*2186*
Apparent peripheral volume of distribution, VpM/F (L)	*5390*	*4772*
TFV first order absorption rate constant from second depot compartment, k_{TFV} (1/h)	*0.171*	*Not estimated*
LPV/RTV effect on relative bioavailability	*2*	*Not estimated*
BCLCRSW effect on CLM/F	*0.588*	*0.413*
Residual proportional error (%)	*45*	*51*
Residual additive error	*1.16*	*1.57*
IIV of CLM/F (%)	*24*	*24*
IIV of VcM/F (%)	*116*	*151*
IIV of VpM/F (%)	*23*	*23*
IIV of QM/F (%)	*56*	*61*

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Source: Adapted from [a]Applicant's response to Clinical Pharmacology IR and [b]Reviewer's independent analysis.

Table 16 summarizes the mean (CV%) for model-predicted TFV plasma exposures for Study GS-US-380-1474 by body weight groups. The model-derived TFV exposures at steady-state for pediatric patients weighing 14 to <25 kg receiving BIC/F/TAF 30/120/15 mg FDC are comparable with those weighing ≥25 kg receiving B/F/TAF 50/200/25 mg FDC.

Table 16 PopPK derived Tenoforvir Plasma PK Parameter Estimates pediatric patients ≥ 3 Years of Age Weighing ≥ 14 to < 25 kg, and ≥ 25 kg and Adults

	Pediatric Patients (Study GS-US-380-1474)	
	≥ 25 kg	**14 to < 25 kg**
N	100	22
AUC_{tau} (h•ng/mL)	343 (28.2)	331 (26.5)
C_{max} (ng/mL)	22.2 (40)	21.2 (30.6)
C_{tau} (ng/mL)	11.4 (28.3)	10.5 (28.4)

Source: Adapted from Applicant's Table 5 (page 22) of Summary of Clinical Pharmacology Studies, and Table 55 (page 81), TAF-TFV peds PopPK report.

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